



# BULLETIN

OF THE NEW YORK  
ACADEMY OF MEDICINE



*Original Articles*

*by*

PAUL D. WHITE

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JULY 1940

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HEART DISEASE—A WORLD PROBLEM\*

PAUL D. WHITE

Lecturer in Medicine, Harvard University

SOLOMON said, "Keep thy heart with all diligence; for out of it are the issues of life" (Prov. 4:23). Those were the days when the heart was the seat of the soul, the badge of bravery, and the abiding place of affection. Far be it from me to assume that the physical heart can rank with such attributes in world history, particularly in the troubled times of today. To paraphrase the scriptures, "For what is a man profited if he shall keep his heart whole and lose his own soul? or what shall a man give in exchange for his soul?" Fortunately in our mission as physicians we are not limited to the mere technical work of diagnosis and impersonal treatment; it is our privilege to dispense courage, sympathy, and an attitude of mind which in themselves fortify our drugs, our diets, and our bloodletting.

In 1618, ten years before Harvey, Albertini wrote a book on the heart, not only the first one on that organ as such, but actually entitled *Affections of the Heart*. Unfortunately the book does not live up to the title except in one particular. He discusses at great length the one chief symptom that was at that time accredited to the heart, namely palpitation, as had been done by many others before him, especially by Galen

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\* The Hermann M. Biggs Lecture, given April 4, 1940, at The New York Academy of Medicine.

and Avicenna; he mentions the fact that all sorts of things can excite the heart to palpitate, both cardiac and noncardiac, that is, that much palpitation occurs without heart disease, which at that time in history was just beginning to be clearly recognized as possible without an early death.

But it is Senac whom I would like to quote in particular, to establish a background for the broad cardiological viewpoint of today. Senac was the first important clinical worker in the field and his writings in 1749 stand out as the pioneer textbook on heart disease based on the physiological and anatomical contributions of Harvey, Lower, and Mayow, and on the reports of cardiac pathology by Bonetus, Vieussens, and Lancisi, during the century that preceded him. There are three points stressed by Senac in the preface of his book two hundred years ago that I would like to stress today as an introduction to the subject of heart disease as a world problem: First, on page xiv, he writes, "The mind is not great enough and life is too short to embrace all anatomy. In spite of all the help of our predecessors it is hardly possible for one man to develop exact knowledge of a single viscus. Those long works which enclose the details of every part of the body announce their own sterility, even by their very extent. They are like maps of the entire world where whole kingdoms appear as dots."

Second, on page xvii, Senac states, "In citing authors I have tried to avoid the national prejudice which dominates even savants. Several imagine that genius and knowledge are attached to their particular country and that the other nations are condemned by nature to sterility. This vanity can be useful to the states; by inspiring confidence and scorn, it inspires courage or rather ferocity, but it degrades the mind. Genius is the property of no nation; it is mingled by chance with stupidity and ignorance. . . . Let those who have the spark be separated by the seas or by the long stretches of the earth, they form a republic whence the rest of mankind is excluded."

And finally, on pages xl and xli, "The heart is a kind of center where all disorders converge. All the ills of the rest of the body reflect on this organ. As soon as some part is irritated or inflamed, the heart may partake of its suffering. . . .

"What are the obstacles against which the heart rises up and rebels, so to speak? Is it some obstruction or a thickening of the blood, irritation, plenitude, or quality of the body fluids? How do such causes,

sometimes so far removed from this organ, trouble its action? . . . We often multiply without reason the sources of our ills; without suspecting the true causes, we give the others added importance.

"We know hardly how we live, but we know still less how we die; what is the cause which stops the heart when a fever leaves no trace of its ravages? . . . One must then seek the causes of death in the outside influences which arrest the movement of the heart, so fragile a bond between soul and body.

"But the heart itself is exposed to various maladies. Observation and experiment are guides which lead us to the source of these ills. The descriptions recorded in many works are too diffuse, and so it has been necessary to separate the factors and to follow them right to the very causes discovered by dissection, to study them, to note their differences, and to relate them to the structure and the action of the organs. . . . The present volume will include therefore a detailed account of the derangements of the heart, which organ is no less limited in the number of causes which trouble its action than in the varieties of this very action itself." . . . Senac ends this very intelligent preface by quoting an ancient author, "Our works are not such as we desire but such as they can be; minds more enlightened than ours will add what has escaped us."

The chief reason why I have quoted Senac at some length is to point out that he had at least the vision of the importance of the diagnosis of heart disease according to cause; structural changes and disturbed action he recognized as secondary to such underlying causes, which, at that time, were very obscure and even today are largely unsolved although they are far clearer as problems to be unravelled. Thus, Senac may rightly be called the pioneer in the modern three-fold diagnosis of heart disease according to etiology, structure, and function.

But before we go further it will be well to pause a moment to state what I mean by the term heart disease. There is a difference of opinion now, as in all ages, about the meaning of the word "disease" itself. Literally dis-ease is discomfort and the word discomfort may be applied to a slight and transient headache the "morning after"; to a little gas in the stomach after swallowing fluids too rapidly; or even to a knock on the crazy bone, or a single extrasystole. It would seem far fetched, however, to call these things disease as we ordinarily use that term. Moreover, Webster's International Dictionary labels as obsolete the definition of disease as discomfort. Even if we grant that the definition of

heart disease as used medically may have a wide range of meaning from the slightest possible and least important transient disorder of function like an extrasystole to the most extensive lesion of the heart compatible with life, we shall only confuse the issue of our present consideration of heart disease as a world problem if we include two particular groups of cases. Like the poor they are always with us and always will be; they comprise practically the sum total of mankind and do not have any important bearing on really significant heart disease. These two groups of cases are in the first place all those who at one time or another have a few cardiac symptoms of neurocirculatory asthenia or a premature beat or two, and in the second place, all those who have very slight changes in the myocardium secondary to a thousand and one diseases which may or may not be fatal in themselves, the myocardial changes such as terminal cloudy swelling having no material bearing on the course or outcome of the disease.

On the other hand, there enter for our present consideration certain well recognized and common kinds of heart disease, such as the rheumatic; a few rarer or more obscure types, such as neoplasm; and occasional effects from various miscellaneous conditions, such as anemia and malnutrition, which when severe can appreciably affect the heart but which in ordinary degree do not cause uncomplicated heart disease.

I cannot sufficiently stress the importance of the etiological point of view about heart disease. It is an old story for some of us brought up under the medical influence of Richard Cabot in Boston or of John Wyckoff and Alfred Cohn in New York, and it fits into the conception of preventive medicine championed so strongly and effectively by the pioneer for whom this lectureship was named, Hermann Biggs of New York City, but it still remains a novel point of view in some parts of the world and even in our own tables of mortality statistics where it should be properly established. There is still talk of cardiac enlargement and failure, of valvular disease and arrhythmias, and of chronic myocarditis as the chief interests of the doctor in his study and care of patients with heart trouble, be he family physician or specialist. This is to liken the function of the medical man to that of the salvage squad after the fire fighters have left—an essential job to be sure but not the vitally important task of the early recognition, and treatment, and prevention of the underlying causes of heart disease. The cardiologist like other members of the medical profession should strive to wipe out the

need of his services; he probably will not be able to do so entirely for it seems likely that the aged will still suffer and succumb to heart disease for generations at least after other mortal ills have been conquered, though even that need not be considered forever insuperable.

It is the family doctor who should be the first to discover the beginnings of disease which may carry heart trouble in its wake and it is he who may also find the actual beginnings of heart disease itself. He should not wait to act till he is confronted by heart failure; he should discover the high blood pressure or the valvular disease or the cardiac enlargement long before failure comes. He may need to call in the specialist for help but his most useful service will be in the attempt to study all the circumstances of the very onset of the causes of the underlying disease and not so much of the resulting heart disease. Anyone with his eyes open may discover important clues, and the important clues in the campaign for the prevention of heart disease are in the very beginnings of the causes of heart disease.

One of the most important points I can make in my discussion this evening is, that in order to shift the emphasis from heart disease to its causes where it rightfully belongs, we should record as the chief diagnosis the causative factor first, and second, the presence or absence of any resulting heart disease, and finally, the degree of heart trouble if present. Thus, instead of diagnosing hypertensive heart disease it is more to the point to diagnose hypertension with or without cardiac enlargement or failure, just as we would diagnose hypertension with encephalopathy or with nephritis or renal failure.

Heart disease is a world problem, as much as is tuberculosis or dysentery or influenza, but it has not yet been investigated as such, in contrast to many of the infectious diseases which have scourged the world, especially in the form of waves of devastating epidemics. It is natural that the rapidly fatal and highly contagious diseases should be studied first and brought soonest under control, leaving for us of the present day the study and control of the less dramatic, more insidious and gradual, but no less fatal maladies such as heart disease and cancer. International coöperation and world-wide study have become the matter of fact procedure in dealing with the serious infections. The pioneer work of the Rockefeller Foundation and other groups transcending national boundaries have broken the ground and shown the way. It should not then be too hard to follow their footsteps in the collection of inval-

able information about the most important causes of heart disease and the incidence and severity of their effects on the heart under all sorts of conditions and in every corner of the globe. Nature has for centuries been conducting gigantic experiments as to the effect of climate, of type of work, of diet, and of local or world-wide diseases on men, women, and children of different races, that are spread out before our very eyes for us to record and to analyze, quite readily yielding information that might never be obtainable by our own experiments on man, although certain tests could be added to enrich the findings. Under the most exacting conditions animal experiments of this sort cannot be completely applied to man; important clues and discoveries can result from experiments on laboratory animals, but if we rely only on them we are letting go to waste an equally important source of information about heart disease.

Statistics from surveys are slowly accumulating in this country and in certain other countries but by different uncorrelated groups, making them often difficult or even impossible for direct comparison. We need a large, well organized study that can in a several year program collect information, not just from hospital clinics or private practice, but from entire communities that will really show how common are hypertension and rheumatic valvular disease and syphilitic aortitis and coronary disease in relation to climate and mode of life. Several well and similarly trained groups armed with good clinical observers, stethoscopes, sphygmomanometers, electrocardiographs, x-ray apparatus, and autopsy technique could in a few years accomplish more than the next century of desultory work, and cost less than a single air raid over a city at war.

Let me take up in more detail what we do know or think we know about the world incidence of the seven important types of heart disease today, first prefacing these observations by a few sentences about the normal heart and the less important kinds of heart disease.

*What is the range of the normal heart?* This to my mind is the hardest question of all and the one most in need of study. No two hearts are exactly alike; even identical twins have different electrocardiograms. We have a fairly clear idea of the average normal figures for pulse rate, blood pressure, heart size, and electrocardiograms at different ages and sizes, but the upper limits of normal and the width of the borderline between normal and abnormal are still in need of clearer demarcation. We are trying, for example, to determine by x-ray some better standard

than height and weight and body surface for the normal heart size; certain measurements of body-build undoubtedly are important and we are asking for the help of the anthropometrists in this study. And the normal electrocardiogram has not yet been completely described. Within the past two years we have discovered to be normal, inverted T waves in Lead 2 due to the effect of vertical position and rotation that once were labelled coronary T waves, and we have found that P-R intervals in Lead 2 of 0.20 or 0.21 second may be normal and not the result of heart block, due to an isoelectric beginning of QRS<sub>2</sub>. These are simply examples of some of the things we are learning almost every day about normal variations. In the world-wide studies will we find that heart size and electrocardiograms and blood pressure vary with race and climate or are they dependent more on body build and mode of life?

*The seven important types of heart disease* that I shall discuss particularly are in the order of their importance first, the more common group, *hypertensive, coronary, rheumatic, and luetic*, and second, the less common group, *congenital, the cor pulmonale, and subacute bacterial endocarditis*. Of the *lesser causes of heart disease* many variations in incidence and degree occur in different countries and indeed in different parts of the same country. *Anemia*, for example, is rife where malaria and such diseases abound and there the anemic heart is fairly common with a variable amount of dilatation and murmurs which simulate valvular disease and in fact have even given rise to an exaggerated estimate of mitral stenosis, and hence of rheumatic heart disease in certain tropical countries. Porter of Richmond has recently made some helpful observations of the anemic heart in Puerto Rico. *Malnutrition* and *avitaminosis* are now widely recognized as possible causes of edema and even of cardiac abnormalities themselves, but in this part of the world such results are uncommon and in the far East, too, they are much less common than they were years ago. In parts of the world where medical advances have been greatest *thyrototoxicosis* no longer plays the role of exhausting occasional hearts that it did a generation ago before there were adequate early diagnosis and effective surgical treatment of thyroid disease. *Myxedema* was always a rare cause of heart disease and today the "myxedema heart" is almost non-existent. Other endocrine cardiac disorders are also rare so far as we now know. *Neoplasm of the heart*, either primary or secondary, is so rare the world over, so difficult



of diagnosis, and so non-amenable to treatment that it may be passed by with this mere mention. *Trauma* of the heart is rare except as the result of attempts at homicide or suicide and in the theaters of war; damage to the heart from accidents, like the so-called steering wheel contusion, is undoubtedly very uncommon but is liable to exaggeration in these days of traumatic neuroses. Practice in suturing wounds of the heart is rare with us in Boston but not so uncommon in certain Southern communities where icepicks and razors are handy weapons with which to settle arguments among the colored folk; and war surgery of the heart will probably receive an extra polish in World War No. 2. Finally, there are scattered through the world certain foci of *infection of unusual nature* so far as the rest of the world is concerned or of an unusual degree of some widely distributed infection. Thus, in Brazil cardiac trypanosomiasis or Chagas' disease has long been recognized as a common infestation of which we apparently see no examples in this part of the world; malarial countries report heart damage in severe cases not to be attributed to the anemia alone; remote regions are sometimes affected by diphtheria or trichiniasis where control is inadequate and the heart may be seriously involved. Further studies of such rare or localized types of heart disease are of more than academic interest to us, but they are not in any way comparable to the importance of the common and widely distributed types of heart disease.

*Hypertension* with heart disease following on its course has been reported now in every part of the globe, even in China, Arabia, and equatorial Africa where it had been thought to be very rare or even non-existent. No adequate statistics have as yet been collected but we do know that hypertension is much rarer in the tropics than in temperate climes and that it seems to have increased in Japan and China since, though perhaps not because of, the introduction of occidental modes of life.

In our own country with widely different climates and races and kinds of work, hypertension is common in apparently every part. Its relative incidence, however, varies, depending largely on the incidence of the other three common types of heart disease. In the Northeastern and Central States where rheumatic and coronary heart diseases are very common, hypertensive heart disease makes up only 20 to 30 per cent of the cardiac cases, but in the South, where rheumatic and coronary types are less common, the hypertensive type makes up 40 to 60 per

cent of the total. Would more extensive studies show that hypertension is fairly common throughout the civilized world, or does the American mode of life play a role? Do the hurry and bustle, the lack of leisure or the failure properly to utilize the leisure we have, and overnutrition play a part? Perhaps not, but I have the impression that hypertension as a disease most common among the most overnourished people cannot be matched by any disease quite so important that is common among poorly nourished people. Perhaps the nomad Arab, even with his malaria and syphilis, can teach us something about health. Lawrence has written of the Arabs' hard physical life and his diet of a handful of dates day after day with a gorging feast on roast mutton every week or two or three. The fast days as well as the feast days may do him good—at least he rarely has hypertension or apparent coronary disease or gall stones or appendicitis or peptic ulcer; so says a keen and reliable observer, the so-called "desert doctor," Paul Harrison of Muscat on the Persian Gulf.

Or perhaps diet and mode of life do not directly influence blood pressure in a serious way; there may be, as revived by Goldblatt, a greater renal factor in one country than another. If so, why? And perhaps such a factor may likewise be in some way connected with diet and mode of life. And where does heredity come in? Perhaps indirectly in the way we live. We certainly need much more light on these problems, and we have not adequately studied even our own communities for comparative statistics on the incidence of hypertension.

Given hypertension, is it better borne by the heart in some peoples than in others? Is the malignant type a characteristic of any particular group of persons?

The second important cause of heart disease, *sclerosis and obstruction of the coronary arteries*, is likewise a subject demanding much more extensive as well as intensive analysis. Available statistics, which are very inadequate, indicate that coronary heart disease is much more common in the white race and in the United States than elsewhere; for example, in our own Southern states more than twice as much was found in the Whites as in the Negroes, and in 1934 vital statistics gave a mortality figure six times greater for the United States than for Japan. In France, however, so Gallavardin told me some years ago, coronary disease is fairly common; he was the first man ever to collect personally as many as a thousand cases of angina pectoris for analysis, and that was in the pleasant valley of the Rhone. Approximately a third of the

cardiacs in our Northern States are listed as coronary in type, while in the South, even among the Whites, the percentage is apparently appreciably less; but satisfactory statistics are lacking.

A few years ago we found that 100 unselected cases of coronary disease under the age of forty showed a very high preponderance of males (96 to 4), and a large majority of overweight, underexercised city dwellers who used tobacco to excess. Which of these attributes are important? Certainly the sex, and yet well known as that is, it has passed with little notice. There must be something in the endocrine setup in the male sex that makes the male much more a target for early coronary disease than his female counterpart in business or professional life. Even if later studies prove this to be true, we may not be able to attack the sex factor itself, but we may be able to alter some of the other factors such as overnutrition and lack of exercise and excessive nervous strain. Is it true that farmers and heavy laborers have much less coronary disease than doctors and lawyers and politicians and business men? In my recollection I can remember having seen only two farmers with coronary thrombosis; the one in Vermont, however, had been a banker for twenty years before he became a farmer, while the one in Maine had quit active farming ten years earlier to travel the countryside in his car as a political appointee. Such data are very unreliable and farmers are notably uncomplaining about their casual ills; a real survey of farming communities with careful questioning and electrocardiography is needed for comparison with a similar city survey to settle the problem which is obviously a most important one. The matter of family and racial inheritance is here intriguing—at one end of the scale is the high incidence among Jews and at the other end, the low incidence among Negroes. Can a person with a high and early incidence of coronary disease among his forbears break the spell by following a special mode of life, or is he doomed? It is my impression that he is, at least to a certain extent, the master of his own fate. Should he move to any particular climate, if he can, or type of community? Should he eat certain foods, low perhaps in cholesterol fats, as advised by Leary and Joslin? How much exercise should he take? And how much rest? How often vacations? How much mental work? Some of these answers we can doubtless get from a world-wide survey such as I have envisaged above.

On the other hand, in this matter of coronary disease and of hyper-

tension, too, there are other things to think of besides heart health alone. There is doubtless possible a compromise between the extremes of valetudinarianism and casual neglect, but there are two quotations in this connection that I would like to read you; they revert somewhat to my comments on Solomon's proverb. The first is from Plato in the *Dialogues* as cited by Osler: "Before the time of Herodicus, the guild of Asklepios did not practice our present system of medicine, which may be said to educate diseases. But Herodicus, being a trainer, and himself of a sickly constitution, by a combination of training and doctoring found out a way of torturing first and chiefly himself, and secondly the rest of the world.

"How was that?" he said.

"By the invention of lingering death; for he had a mortal disease which he perpetually tended, and as recovery was out of the question, he passed his entire life as a valetudinarian; he could do nothing but attend upon himself, and he was in constant torment whenever he departed in anything from his usual regimen, and so dying hard, by the help of science he struggled on to old age.

"He goes on to say that Asclepius did not instruct his descendants in valetudinarian arts because he knew that in well-ordered states individuals with occupations had no time to be ill. If a carpenter falls sick, he asks the doctor for a 'rough and ready cure—an emetic, or a purge, or a cautery, or the knife—these are his remedies.' Should anyone prescribe for him a course of dietetics and tell him to swathe and swaddle his head, and all that sort of thing, he says, 'he sees no good in a life spent in nursing his disease to the neglect of his customary employment; and therefore bidding good-bye to this sort of physician, he resumes his ordinary habits, and either gets well and lives and does his business, or, if his constitution fails, he dies and has no more trouble.'"

The second quotation is from Edna St. Vincent Millay:

"My candle burns at both ends;

It will not last the night;

But ah, my foes, and oh, my friends—

It gives a lovely light!"

And yet one need not insist on dying with one's boots on.

Our third main problem is *rheumatic heart disease*. Here too the fundamental cause is unknown, and the incidence of the disease through the world very inadequately explored, but there are some things about

it that are clear to us today. In the first place, it is most common among the poor people where the living conditions are worst in any given community—there is no doubt about that. Secondly, there is a fairly high familial incidence. Thirdly, it is much more common, at least in severe form, in the temperate than in tropical climates, and its incidence increases steadily, other things being equal, from south to north in the temperate zone of the Northern Hemisphere and from north to south in the Southern Hemisphere. Fourthly, *Streptococcus hemolyticus* throat infections are particularly prone to set off an acute rheumatic infection. Fifthly, this rheumatic infection leaves a damaged heart in 75 per cent of the children who have it in New England, very preponderantly the highest incidence of heart disease resulting from any infection in this part of the world. And finally, the acute rheumatic infection or reinfection is more often responsible than any other factor for cardiac dilatation and myocardial failure in rheumatic heart disease, apparently at any age. From the standpoint of world-wide studies, here are three important facts already established but not adequately studied, namely, the effect of living conditions, the effect of climate, and the effect of streptococcus infection as the chief exciting factor. It may well be that the last two mentioned facts are directly related, namely, that the lower incidence of *Streptococcus hemolyticus* infections in the tropics is responsible for the lower incidence of serious rheumatic heart disease there.

Despite this knowledge there are occasional surprising discoveries. For example, I was amazed to come across numerous cases of acute rheumatic heart disease in the Cardiac Clinic of the General Hospital in Mexico City two years ago this month in most beautiful climate and ideal mild weather. I thought the altitude of 8,000 feet might have something to do with this but the doctors told me that some of the cases came from the lowlands at sea level along the coast in really tropical country. One might perhaps blame poor living conditions, for these patients were almost wholly native Indians who lived for the most part in rather primitive ways. But a fuller analysis of those findings is in order. Incidentally I also discovered that *Streptococcus hemolyticus* throat epidemics were by no means rare in Mexico City and the surrounding countryside—one was in progress while I was there. To various medical friends of mine in the United States these observations were as complete a surprise as to me, showing how ignorant we are of

what goes on not only in our own hemisphere, but even on our own continent and at our very door.

In New England, and in the Rocky Mountains, at least a third of all the cardiac patients are rheumatic in type. New York, Illinois, Iowa, and Minnesota have about the same or slightly less; Virginia, West Virginia, the Pacific Northwest and California have distinctly less, between 20 and 25 per cent; Texas, Tennessee,\* and Oregon have been reported as having 10 to 15 per cent; and the Negroes in the Southern States as having 5 per cent or less. One of the most interesting observations of all has been that of Paul and Dixon who reported in 1937 that rheumatic heart disease was almost ten times as frequent among western Indians living in the cold, relatively dry regions of Wyoming and Montana close to the Canadian border, as it is among similar groups living close to the Mexican border (in the warm dry climate of southern Arizona). Thus climatic conditions seem to supersede race in susceptibility to rheumatic heart disease. Nearly 1 per cent of the school children of Boston, New York, and Philadelphia a few years ago had rheumatic heart disease while only one-sixth of that number were so affected in San Francisco and one-third in Cincinnati.

Apparently England has as much rheumatic heart disease as we have hereabouts and as many as 26,000 new cases of rheumatic fever annually have been reported for Scotland. On the continent of Europe, however, it is said to be not so common, with perhaps the incidence found in Virginia, and much rarer as one travels eastward (Pines tells me that the ratio of rheumatic heart disease to hypertension in Poland is about 1 to 50). In Arabia Harrison has encountered only a few cases of rheumatic heart disease each year. In India it is not rare, but some cases of anemia there had at first been wrongly called mitral stenosis. In China there have been conflicting reports but it seems likely that there are more cases in the North than in the South. In Australia a low incidence of rheumatic heart disease is reported and in the West Indies and in Venezuela it is said to be very rare. An accurate world-wide survey of the incidence of the rheumatic infection and of rheumatic heart disease is in order, for here, even more than in the case of hypertension and coronary disease, the practice of preventive medicine appears possible in the future.

\* A recent paper (Swanson, H. Combined Syphilitic Aortitis and Rheumatic Disease of the Heart. *Am. Heart J.*, 1939, 18, 672) reports the finding of about as much rheumatic heart disease as syphilitic aortitis at Nashville.

The last of the common types of heart disease, *cardiovascular syphilis*, in reality luetic aortitis, is no longer common with us in New England. Under our very observation it has apparently halved in its incidence in the last 25 years, from about 4 per cent of cardiac patients in the community at large to about 2 per cent, and in private practice to less than 1 per cent. Autopsy figures give a higher incidence, but at least half of the cases showing aortitis at autopsy have only a slight non-clinical degree, active or inactive. I have found in my efforts to establish a good teaching collection of pathological specimens from autopsies in my private practice that among the hardest to obtain because of their rarity are illustrations of luetic aortitis.

It is, of course, well-known that in some parts of this country and elsewhere in the world cardiovascular syphilis is common, several times, at least, more common than in my own experience noted above, and comprising as many as 32 per cent of one series of Negro cardiacs in Texas, but even so there are some interesting facts that are not so well known, and a number of questions to be answered. Among the Negroes in the South aortic syphilis is quite common but not so common as is hypertensive heart disease, which rated as high as 51 per cent of the Texas Negro cardiacs referred to above. Also, the high incidence of aneurysms and of comparatively early deaths of the Negroes with aortic syphilis may be ascribed not alone to their neglect of specific therapy but to the nature of their work; heavy labor is their common lot and that is not the best treatment for a weak aorta or a stretched aortic ring. In this connection some comparative statistics of the health of soldiers is of interest. In 1870 Myers, Surgeon to the Cold Stream Guards of the British Army, published a prize essay on the soldier's heart and stated that one British soldier per thousand in the service died of aortic aneurysm in the 1860s—he incidentally blamed chiefly the tight collar of the army uniform for this high incidence. Contrast this with the report of the Surgeon General of the United States Army for 1938, seventy years later, in which it is recorded that only one man out of 175,000 officers and men died as the result of an aortic aneurysm. Myers might have said, had he known what would happen, "You see what the change to a comfortable uniform has done." Another interesting fact is that in some parts of the world syphilis is apparently so attenuated in its effects that serious aortic involvement is rare. In Arabia, for example, where syphilis is almost universal, Harrison states that he had

encountered only three aortic aneurysms in 25 years. Thus there seem to be two diametrically opposed groups where luetic aortitis of clinical importance is low in incidence: one, the community where syphilis in the first place is not a very common disease and when it does occur is quickly diagnosed and adequately treated, and the other, the place where syphilis has been present in almost every one for generations and little or no treatment has been taken. There are other interesting relationships that need further enlightenment but it is obvious now that cardiovascular syphilis is not only a preventable disease but that we are living in the course of its actual prevention.

The first of the lesser causes of heart disease is that of the *congenital anomalies*, making up 2 per cent or more of all our cardiac cases and 10 to 15 per cent of cardiac school children\* in New England and about half of the cardiac children in San Francisco. Since, however, the incidence of rheumatic heart disease is much lower on the West Coast than in New England, it seems probable that congenital heart disease occurs with about the same frequency in both places. Thus, the congenital heart figure of 1/7th of the 1 per cent incidence of the total heart disease found in the school children of Boston is to be compared with the 1/2 of the 1/3 per cent incidence in San Francisco. It is possible that the incidence is the same the world over, but of that we have no assurance whatsoever. It would indeed be of interest to know. One of the chief reasons why statistics of congenital heart disease have been slowest to accumulate is the difficulty of diagnosis that held sway everywhere until recent years and still rules today in most parts of the world. However, in the most enlightened communities great progress in diagnosis has been made in the last generation, greater in fact than in the case of any other type of heart disease (except so far as the occlusion group of the coronary type is concerned). After the first year of life not only has the diagnosis of congenital heart disease become relatively easy, but even the differentiation of the various anomalies has become possible in the majority of cases. It is in the first year that the greatest difficulty remains and it is in that same year that a large percentage of these children die, estimated at about 50 per cent at the Children's Hospital in Boston; such are the cases naturally with the gravest anomalies.

It once was said that it is idle to bother with congenital heart disease

\* If young infants are included in estimating the incidence of congenital heart disease among the cardiac children in New England the ratio of congenital to rheumatic heart disease is about 1 to 4, instead of 1 to 10 or more, as noted in the older children.



because of the impossibility to prevent it, the difficulty to diagnose it, and the absence of any treatment for it. Not only are these prophets being shown to be in error as to diagnosis, but treatment, too, is developing, as witness the growing number of cases of successful ligation of the patent ductus arteriosus and the increased longevity of even very serious cases by methods of special care. It is also conceivable that in the future there may even be a reduction of intrauterine infection or other diseases, or of defects of germ plasm responsible for congenital anomalies of the heart.

The second of the lesser causes of heart disease is the most serious of all—*bacterial endocarditis*. Included here are both acute and subacute infections and all sorts of bacteria but only one of the lot ranks as important, namely the *subacute Streptococcus viridans endocarditis*, because the acute cases are almost always superimposed on fatal infections elsewhere in the body, such as pneumococcus pneumonia or staphylococcus septicemia, and are rarely diagnosable terminal processes, while subacute infections by other than the *Streptococcus viridans* are very rare. However, at the outset it should be recognized that the *Streptococcus viridans* itself is not just one simple strain; it is made up apparently of a whole variety of strains which not only react differently to different individual hosts but also react differently to different chemical agents. This fact is especially important now because of the recent introduction of a whole series of new chemotherapeutic agents which range all the way from the original sulfanilamide through sulfapyridine, sulfathiazole, and sulfamethylthiazole to the newest preparation of all, sodium paranitrobenzoate, just reported at meetings in New Orleans as being more or less specific for this very organism, *Streptococcus viridans*.

Subacute bacterial endocarditis is almost invariably engrafted on congenital or rheumatic heart disease, causing death in some 10 per cent of the former and 5 per cent of the latter. Its incidence in New England is about 2 per cent of all cardiac cases and in most other parts of the world, where the rheumatic heart is less common, subacute bacterial endocarditis is also rarer; but we possess very inadequate data about its frequency the world over.

The great dread of this type of heart disease is due to its almost invariably fatal ending after a long drawn out miserable illness lasting on the average six months. For many years, in fact ever since the disease was first recognized, innumerable physicians have watched thousands of

patients slowly die, unable to do anything to save them; about one in a hundred recovered, more or less spontaneously. In the last year or two the picture has begun to change and a few patients are still alive and in fact seem quite well, months longer than it appears likely they would have been in the old days, as the result of the administration of the new chemotherapy already mentioned, with the possible additional aid in some cases of the effect of heparin in reducing the number or size of endocardial thrombi. It seems possible that we are at the dawn of a new day in the treatment of this dread disease; it is not alone a reduction of mortality that is being effected but a control of the severity of the disease in many of the uncured cases. The next few years will witness a crucial struggle against this infection which should be waged the world over.

Finally, we come to a very difficult but intriguing problem, the incidence of the *cor pulmonale*, or heart disease secondary to disease of the lungs or of their blood vessels (pulmonary heart disease). Even in the most advanced medical centers we have no exact information as yet. The reason is that high disabling degrees of the condition are apparently rare and one must make unusually careful measurements of the muscle bulk of the right ventricle (in the absence of failure of the left ventricle) to pick up the lesser grades. Undoubtedly in these lesser but unimportant grades the chronic *cor pulmonale* is not so rare as it was once thought; Scott has found this to be true recently in Cleveland. On the other hand there has been a good deal of confusion caused in the past by mistaking the symptoms and signs of the underlying pulmonary disease itself for evidence of heart failure secondary to such lung disease, with lack of realization of the simple fact that when the right heart fails, the chief evidences of such failure are to be found in elevation of the systemic venous pressure with engorgement of neck veins and liver, and not in congestion of the lungs. As the result of these various difficulties we know next to nothing about the true incidence of the *cor pulmonale* the world over or even of the amount of its severer grades. We do know that in certain mining communities and perhaps in certain countries where extensive pulmonary disease is frequent, the *cor pulmonale* is much more common than in other parts. With us in New England apparently no more than one in fifty cardiac cases has the *cor pulmonale*; in some parts of the world, where rheumatic and syphilitic heart diseases are not frequent and silicosis is common, the proportion

of cases of the cor pulmonale might easily be many times greater. The field for this study is wide open and it is obvious that preventive medicine, so far as the cor pulmonale is concerned, has a promising future. Fortunately the so-called primary pulmonary endarteritis obliterans as a cause of right ventricular strain is a rare curiosity—I can recall having seen, to recognize, only three cases in the last twenty years.

Before leaving this discussion of the types of heart disease it should be noted first, that many cases show combinations of several factors, particularly of hypertension and coronary disease, and of rheumatic scarring and *Streptococcus viridans* infection, and second, that it is occasionally impossible to fit every case into any one or two pigeon-holes—we must leave open a space for unknown etiology which may even allow our curiosity to establish new types in the future or to clarify causes that are at present obscure. Is it possible, for example, that repeated or prolonged paroxysms of excessive tachycardia may result in slight or progressive enlargement of the heart even leading to eventual failure without the intervention of well-recognized factors of heart disease? We know that in infants extreme tachycardia may cause cardiac dilatation and failure, which may even be confused with what used to be called congenital idiopathic hypertrophy of the heart. The effects of high altitude and of prolonged excessive physical effort on the heart of man have also been inadequately studied as yet and the question too of individual or even racial differences of myocardial resistance to strain, which brings to the front again the old story of the athletic heart.

Having presented the specific problems of heart disease, I shall now put them together as the total problem, a far less significant survey, since we are then simply lumping together different diseases as they happen to affect one organ. Nevertheless, for the sake of completeness we should briefly survey the problem as a whole. Heart disease in toto easily heads the list of causes of mortality in the United States, with cancer second, while the former leaders of thirty years ago, tuberculosis, infantile dysentery, and pneumonia, have dropped to a good deal less than half their former rates; this drop in the infectious diseases undoubtedly accounts for the remarkable drop in death rate in Massachusetts from 60 per thousand in 1910 to less than 20 per thousand in 1934. And yet if we take any single one of the different types of heart disease, which are really distinct non-related conditions, it falls well

down the list, imposing though the whole collection may be.

An interpolation should, however, be made at this point concerning hypertension. This is really a disease in a class by itself because of its far reaching effect on various parts of the circulation; if it does not kill by heart failure it is likely to do so by apoplexy or by renal involvement. If we take from the 1932 United States Mortality Statistics the figures for cerebral hemorrhage, 95,000 deaths and two-thirds of the cases of chronic myocarditis, 60,000, and about half of the chronic nephritis, or 46,000, we undoubtedly have not far from a fair approximation of the cardiovascular effects of hypertension, something over 200,000 deaths, much more imposing than any other grouping except the total figure for diseases of the circulatory system, 295,000 (which does not include cerebral hemorrhage or chronic nephritis). It far transcends the so-called entity of arteriosclerosis. Cancer was only 129,000 and tuberculosis but 75,000. This is another illustration of the value of separating the causes of heart disease for consideration on their own, as we have already done in this paper, but which is very inadequately done in the routine mortality statistics—a reform here is in order and the vague terms acute and chronic myocarditis should be replaced by more accurate designations, such as hypertensive heart disease, or myocardial infarction, or cardiac enlargement of unknown cause. It has been my experience that the great majority of cases of so-called myocarditis can be subdivided into 1) big hearts due to hypertension, 2) coronary heart disease, and 3) neurocirculatory asthenia.

In 1932 the total death rate for the whole United States was 10½ per thousand. Twenty-three per cent of these deaths were recorded as due to disease of the circulatory system, too low a figure undoubtedly since cerebral hemorrhage and chronic nephritis are not included. It is of especial interest to note that there was a considerable variation in this percentage between the Southern and Northern States, with but relatively little variation in their death rates; the Southern States gave figures consistently under 20 per cent, dropping as low as 12 per cent in Mississippi (this figure, by the way, held also for Hawaii), while the Northern States were consistently over 20 per cent, rising as high as 30 per cent in Massachusetts.

A quarter of a million persons in the United States were recorded as having died from heart disease in 1930, more than half of whom (140,000) succumbed before they were 70 years old. That's where

the rub comes. It should not worry us much, in fact we would rather be content, if all the deaths in the United States were from heart disease after the age of 75 with little or no earlier crippling from the condition. This would be a good way out for us. But it will, I fear, be a long time before we reach that goal. The prolongation of the average life in this country in the last hundred years has been amazing, doubling itself in that length of time to an age now well over sixty. That next decade, however, is bound to prove the greatest hurdle, and we can't jump it until we have done more than we have to date with the control of hypertension, coronary disease, rheumatic carditis, and syphilitic aortitis. The factor of syphilis is definitely on the decline, the rheumatic infection seems also to be less serious; although we have some idea of what to do to check these things, we must not relax our efforts one iota. It is, however, against hypertension and coronary artery sclerosis, especially as they affect youth and middle age, that we must now direct our newest attacks. It is in our own country that these diseases seem most rampant and yet one often hears the boast of our prowess in preventive medicine. Do not let us delude ourselves into thinking that we are so healthy while we harbor these insidious but serious evils right in the very centers of our most advanced civilization, in fact in the very hearts of our own medical profession and public health organizations. The challenge is before us: "Physician, heal thyself." It seems to me that while we have been doing fine work in the control of infections and industrial diseases of all sorts in the past generation or two, we have neglected the most simple rules of health laid down through the ages, which balance exercise with rest, overeating with fasting, and excitement with relaxation, not a humdrum life at all but a most rational one for body, mind, and soul. The ancients got fat and nervously exhausted doubtless, but food was not so plentiful for everyone as it is now, chariots were relatively few, and not many of them travelled as fast as the slowest antique motor car at its slowest speed today. I can't escape the conviction that if our present generation used its intelligence and its legs more, and its alarm clocks and its stomachs less, we might have fewer cases of the coronary disease and of the hypertension that so beset us. However, until we have more accurate world-wide information about these things than we possess today, this conviction of mine must continue to be rated simply as an impression, attractive as it may be, on the basis of our clinical observations and of deductions as to the

Creator's plans of the function of muscles, nerves, and circulation.

Let me close with a quotation from Hermann Biggs himself. In 1904 in an address on *Preventive Medicine* before the fifty-fifth annual session of the American Medical Association at Atlantic City he said, "The terms sanitary science, public or state medicine, and preventive medicine have frequently been used as almost synonymous. The latter term, 'preventive medicine,' however, has sometimes been restricted in its application to the prevention of the infectious diseases. In the broad sense, preventive medicine comprises both general prophylaxis and individual prophylaxis, and applies to all forms of disease, not simply to the infectious diseases. Preventive medicine is an applied science, which deals with the preservation of the health, both of the individual and of the community.

"No subject more vitally concerns the welfare of a community than that pertaining to its healthfulness. How the inhabitants live, and how and at what age they die, what is the extent and character of the morbidity occurring among them and what are its causes, are questions of momentous importance. They are essential features in the problem, whose solution will teach men how they may live longer, healthier, and therefore happier lives."

The author then discusses at some length the prevention of the infectious diseases but ends the article with the following remarks:

"A very difficult problem arises in connection with the diseases of the circulatory apparatus and the kidneys. My investigations have shown that in New York City a large increase has taken place, due to these causes, during the last twenty years. The acute respiratory diseases, cancer, and diseases of the circulatory apparatus and the kidneys are the only important causes of death which have shown an increase during this period. The increase in cancer amounts to about 15 per cent, and the increase in acute respiratory diseases amounts to about 15 per cent, while the increase in the diseases of the circulatory apparatus and kidneys combined equals about 40 per cent. In making this statement I have taken fully into consideration the possible influence of greater accuracy in the death returns, i.e., the inclusion formerly of these under other causes of death; but after making all allowances, it seems to me without question that an increase equaling 40 per cent has taken place." [Quite possibly some of this increase lamented by Biggs was due to his already effective prevention of some of the infections of early life

which was allowing relatively more persons to reach heart disease ages, as Drs. Bolduan and Cohn have pointed out.]

Biggs proceeds: "A very important sanitary problem is here presented to the health authorities. *What are the factors in the lives of the inhabitants of our large cities (for I have found that similar increases, less extensive, however, have taken place in London, Paris, and Berlin) which have caused such a remarkable increase in the prevalence of these affections, and how are these factors to be removed?*" [Italics mine.]

Thus Biggs already clearly recognized this problem of heart disease as one of preventive medicine, with world-wide significance 36 years ago. Can we answer his question? No, I believe not, except in minor details, but we have I hope a much clearer conception of the problems left to solve than was possible a generation ago. Vital leadership in finding the path has come from your own pioneer New York Association for the Prevention and Relief of Heart Disease and from the individual labors of Haven Emerson and many others who right here in New York accepted the challenge that Biggs laid down in 1904. I feel confident that much faster progress can be made during the generation that is to come than was possible in the generation that is past. *Tempora mutantur nos et mutamur in illis.*

## THE MENOPAUSE\*

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THE *climacteric* may be defined as that transitional period in women during which cyclic ovarian activity, resulting in menstruation, undergoes cessation. The term *menopause*, strictly speaking, refers to the actual cessation of ovarian activity. The problems arising as a result of this transition extend beyond quiescence of ovarian activity into the *post-menopausal* state. The endocrinological aspects of the problems arising at this period encompass, therefore, all three phases. While generally a spontaneous phenomenon, the menopause may be induced or accelerated by measures which depress ovarian function, such as radiation, or by the removal of the uterus or ovaries, or both.

Although the loss of ovarian secretion is the most important single event and initiates the series of changes which occur at this period, the climacteric must be recognized as a symptom complex involving the readjustment of the whole organism to a new type of internal environment. A change in the balance of the secretion of the ductless glands plays an important part in the reconstruction of this internal environment. Little is known of the exact nature of these changes. That the physiology of the thyroid is at least temporarily altered is apparent from the fact that nodular hyperplasias appear in larger numbers; that this is the age period with the greatest incidence of thyroid atrophy with myxedema; and that the development of Graves' disease is often an accompaniment. A change in the physiology of the pituitary manifests itself in an increased secretion of gonadotropic hormone. The alterations in the other ductless glands accompanying or resulting from the diminution of ovarian activity still remain obscure.

Other biological changes also make their appearance. The climacteric ushers in the decrescent phase of the life cycle of the organism during which the various processes of aging are accelerated and degenerative

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phenomena become correspondingly prominent. These are seen, for example, in the sclerotic vascular changes, in the development of hypertension, and in the degenerative changes in the various viscera and external structures of the body and in the skeleton.

On the psychological level there occurs, likewise, a reorientation of the woman to a new status in relationship to her environment and to her family. Various psychological disturbances ranging from psychoneuroses to the psychoses, of which involutinal melancholia is an important example, make their appearance.

The complexity of the menopausal state is apparent and it has only been possible, since the estrogenic hormones have been available, to begin to differentiate between the phenomena due to ovarian insufficiency and those which are part of an even more fundamental rhythm in the life cycle of the species. The chief purpose of this paper is to examine those phases of the menopausal state for which ovarian insufficiency is largely responsible.

The cessation of menstruation at the menopause appears to be a consequence of the gradual aging of the ovary. The Graafian follicles gradually degenerate and disappear, the blood vessels undergo medial thickening with narrowing of the lumen, and fibrosis of the capsule with contraction, occurs. Watson, Smith, and Kurzrok<sup>1</sup> have shown the increasing insensitivity of the human ovary to gonadotropic stimulation with advancing age. The hormonal effect of these degenerative changes is a significant decrease in the production of estrogenic hormone. Concomitant with this is the appearance of gonadotropin of pituitary origin in the urine in far greater amounts than is ever seen during the normal menstrual cycle, during which it can only be detected for brief periods in the course of each cycle. An adjustment must be made to this new hormonal environment of which only these two aspects are known and which must be considered a physiological one for the species. The majority of women manage this successfully; those who are unsuccessful suffer as a consequence a variety of symptoms detrimental to their well-being. No certain knowledge exists as to the physiological influences which promote and those which interfere with this readjustment. Certainly, with respect to the known hormonal changes, there is no detectable difference between the women who adjust successfully and those who fail and we know of no other satisfactory criteria which differentiate between them.

The suggestion has been made that the symptomatology of the menopausal syndrome is due to an excessive production of gonadotropin on the basis of the observation that estrogenic therapy with symptomatic relief is accompanied by a marked reduction in the excretion of urinary prolactin. However, Heller and Heller<sup>2</sup> were able to dissociate the symptomatology of the menopause and the concentration of urinary prolactin. Their findings are in accord with similar experiments in our laboratory.<sup>3</sup> We must look elsewhere, then, for the factors responsible for this maladjustment.

The treatment of the menopause has made rapid strides in the past few years due to the brilliant work of the chemists who have provided us with specific and powerful estrogenic agents. The problems relating to the climacteric are, however, not solely the province of the endocrinologist and psychiatrist; organic changes in the reproductive tract should not be neglected.

The climacteric may proceed uneventfully and be characterized by a gradual waning of menstrual flow and by cycles otherwise normal. Menstruation may also cease abruptly with no preceding irregularities. Frequently, however, the transition is a stormy period marked by menstrual irregularities, menorrhagias and metrorrhagias which may precede the menopause by many years and offer diagnostic and therapeutic problems. The woman is now entering the age of the greatest incidence of carcinoma, hence such irregularities and bleedings gain significance. One cannot stress too much the desirability for careful gynecological examinations under such circumstances and I feel that it is a necessary precaution to insist that no endocrine therapy be instituted until the gynecologist can assure one of the absence of pathological changes and has corrected any inflammatory lesions, particularly about the cervix, which are felt to predispose towards the development of neoplasms.

#### SYMPTOMATOLOGY OF THE MENOPAUSE

Symptomatology of the menopause is as bizarre and extensive as any syndrome with which I am acquainted. There are certain classic and well-recognized complaints which are most common and a second group of signs and symptoms which occur less frequently but are apparently specifically related to this state. Among the most common symptoms are the vasomotor, with the characteristic hot flush followed by drenching sweats, and the dizziness, palpitation and exhaustion which follow

the attacks. There are also the disturbances of peripheral circulation which take the form of paresthesias and numbness. Insomnia is frequently complained of and asthenia may be profound enough to prevent the patient from carrying out her duties, both domestic and social. In addition, there are a variety of gastrointestinal symptoms largely of functional character. One of the most uncomfortable complaints is of headache. Arthralgias and degenerative changes in various joints contribute to the picture. Changes are noted in the texture of the skin and subcutaneous tissues. Occasionally such phenomena as urticaria and angioneurotic edema are seen. With time, senile atrophic changes occur in the genital tract with attendant discomfort. In many patients there is a definite tendency to gain weight and to become aware of fat deposits different from those seen in early life. On the behavior level, the woman tends to become depressed, emotionally unstable, irritable and given to weeping. She is inclined to withdraw more and more into herself, feel insecure and become hypochondriacal, resentful and suspicious. Other psychoneurotic manifestations may make their appearance or be exaggerated. The sexual life may wane in intensity although occasionally this period is associated with increasing sexual interest. Frank psychoses may be initiated.

Although these symptoms, which could easily be supplemented by many others, generally make their appearance on the cessation of menstruation, they are frequently seen during the period of transition. At this time it is not uncommon for them to be more marked premenstrually when estrin production is at its lowest and to improve or disappear with the development of the ovarian follicle during the first half of the cycle when the production of estrin is increased.

#### CHOICE OF THERAPEUTIC AGENTS IN THE TREATMENT OF THE MENOPAUSE

The proper therapeusis of any disturbance of the ductless glands is dependent on the availability of specific secretions of the glands involved and on objective methods to guide their use. The first of these criteria is fulfilled with respect to the secretions of the ovary. At present there are available three estrogenic hormones of known chemical structure and potency. These are estrone, which is the ketohydroxy estrin; estradiol, the dihydroxy estrin; and estriol, the trihydroxy estrin. Differing widely in their estrogenic activity by weight, equivalent results can be

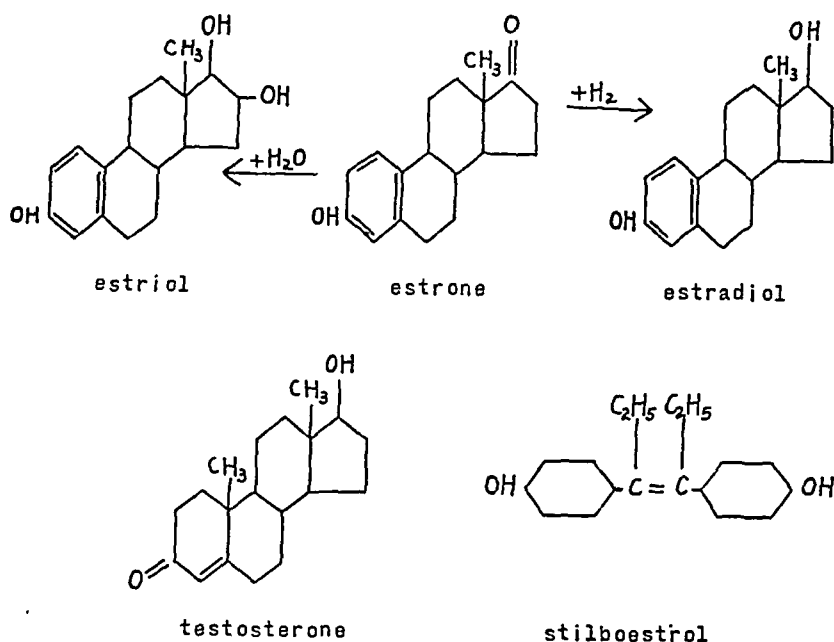


Fig. 1—Hormones used in treatment of the Menopausal Syndrome.

obtained with all, provided adequate amounts are administered. I have found estrone and estradiol to be the most effective and economical for replacement therapy in the human. Estriol preparations are designed for oral administration and should prove equally useful once they are made available at reasonable cost in sufficient potency. Estradiol is usually conjugated with either benzoic or propionic acid in an effort to prolong its activity. These estrogens are standardized in terms of rat and international units, the rat unit being derived from biological assay usually according to the method of Allen and Doisy. On the basis of their biological assay in the human, we have come to rely on the activity expressed in rat units, as the various estrogenic preparations we have analyzed have corresponded to each other in potency rather better on the basis of the rat unit than on the international unit. In addition to the natural estrogenic compounds, two synthetic estrogens have been employed, stilbestrol and ethinyl estradiol; and, interestingly enough, the androgenic hormone, testosterone, conjugated with propionic acid, has proved itself an agent capable of ameliorating menopausal symptoms.

The second criterion, objective methods for the applications of these therapeutic agents, has also been fulfilled to a large extent. Several



Fig. 2—A characteristic menopausal smear prior to treatment with estrogens. Note small oval "deep" cells, undifferentiated squamous cells with large nuclei, cell clumps, bacteria, smudgy appearance, and absence of cornified cells.

possible indices can be employed. It has been suggested that, since the estrogens reduce the initially high titer of urinary gonadotropin of the menopause, the disappearance of this hormone from the urine might serve as an index of full replacement therapy. The disadvantages inherent in the use of this method are that it is laborious and still far from exact. Furthermore, the appearance and disappearance of urinary prolactin in relation to symptomatology<sup>2</sup> and vaginal smear changes<sup>3</sup> have been found to be inconstant and unreliable. The estimation of an elevation of the estrin level in the urine following replacement therapy is also a laborious and time-consuming procedure. Endometrial biopsies to detect

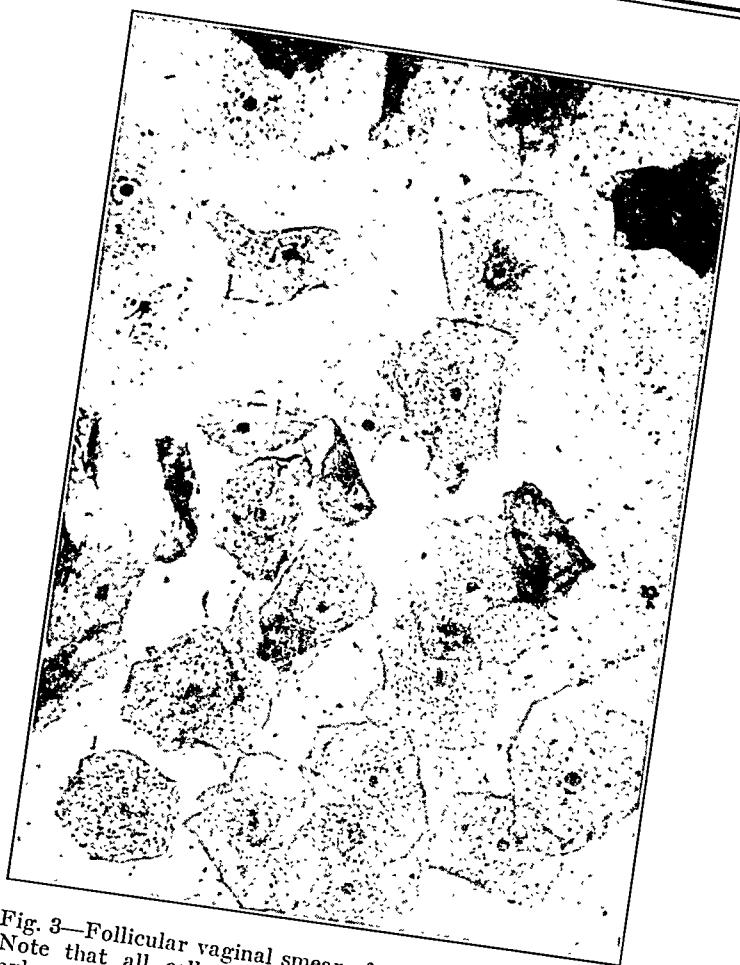


Fig. 3—Follicular vaginal smear after estrogenic therapy. Note that all cells are typically cornified, with small pyknotic nuclei, discretely arranged in a clear field free of debris. This represents the peak effect of replacement therapy with estrogenic hormones. When this smear picture is attained, all symptoms due to ovarian insufficiency *per se* should disappear. (Papanicolaou and Shorr, Reference 4.)

estrogenic effects are associated with trauma and are inconvenient to obtain with any frequency.

In 1935,<sup>4</sup> the vaginal smear was introduced as a method for evaluating the effect of estrogenic hormonal therapy in the human. During the menopause, as a result of the low estrin production, the vaginal epithelium undergoes considerable atrophy. The desquamated vaginal secretion, when aspirated by a simple glass pipette, placed on a slide and stained, reflects faithfully the state of the vaginal epithelium. During

the menopause, it presents a typical picture, quite different from that seen during the normal menstrual cycle. It is free of cornified cells, the squamous cells are of the intermediate type and there are varying numbers of small, round or oval cells from the deeper layers of the epithelium. Bacteria, leukocytes, cellular debris and occasionally red blood cells are to be seen. The smear presents a "smudgy" or "dirty" appearance. When estrogens are given in adequate amounts a series of changes takes place in the smear until it is transformed into one similar to that seen mid-menstrually in the normal cycle. This induced follicular phase is characterized by the presence of cornified cells which are usually discrete, by the absence of leukocytes and debris, and by a clear appearance. At this stage, which represents the peak effect of estrogenic therapy, all of the symptoms due to ovarian insufficiency per se should disappear whereas those of other origins will persist.

This method has the virtue of simplicity, specificity and the absence of trauma. In addition, it can be repeated as frequently as desired. By its use in man it has been possible to assay biologically the variety of estrogenic compounds available and to set up standards for their use. We had hoped by this method to arrive at a definite biological unit for man which would represent a full replacement dose just as the rat or mouse unit is equivalent to an estrogenic unit in these rodents. Had this been possible the therapy of the menopause would have been greatly simplified. We found, however, that individual patients varied greatly in the amount of hormone necessary to produce an equivalent biological effect. Though the "human" unit lay between 2,000-3,000 R.U. daily for most patients, a spread of as much as 1000 per cent, as from 1,000 to 10,000 R.U. daily, was observed. Therefore, as regards dosage, each patient becomes an individual problem.

It also became apparent that menopausal symptoms in different patients were not uniformly sensitive to estrogenic therapy. In about one-fourth of the patients symptomatic relief occurred with relatively little change in the vaginal smear; with about one-half, relief was experienced at intermediate levels; and with the remainder, complete relief was not obtained until full replacement and a follicular smear were achieved. With this, as well as all other objective indices employed, there is apparently no absolute correlation with symptomatology. The smear does, however, have particular value in dealing with the variety of bizarre menopausal symptoms, especially those of a psychoneurotic character,

since by insuring complete estrogenic replacement, it permits a differentiation between those complaints specifically due to ovarian insufficiency and those arising from other causes.

Given effective therapeutic agents and objective methods for guiding their use, we must now consider how best to apply them to the problems presented by the menopausal syndrome. There are two major therapeutic objectives, one is to abolish the complaints which result from failure to adjust to the new status; the other, to achieve as rapidly as possible a satisfactory adjustment which will free the patient from further need of such exogenous support. This program must deal with questions of dosage, the modes of administration as regards effectiveness, convenience and economy, the possible dangers of neocarcinogenesis, the influence of therapy on the eventual readjustment, and the problem raised by the effects of estrogen on the endometrium.

To some of these questions there are fairly satisfactory answers. To others, our present incomplete knowledge permits of no final conclusions.

Much can be said with certainty as to the choice of preparations and the modes of administration. Those estrogenic agents which have proved effective in man have been discussed above. The choice of the mode of administration is largely an economic problem. Estrogens are at present generally employed by the intramuscular route because this is the least expensive. They are also effective by mouth but as they lose so much of their activity by this route, from 10 to 20 times the parenteral dose must be given to obtain the same estrogenic effect. This loss of efficiency by mouth should be kept in mind when transferring from the parenteral route, and it would be desirable to have all estrogenic preparations designed for oral administration standardized in terms of actual activity corrected for this loss of potency. One such preparation is so labelled. The topical application of estrogens in pessary form for the discomfort associated with senile vaginal changes is the accepted method of dealing with this condition. In addition to these routes, Bishop<sup>5</sup> and Salmon, Walter and Geist<sup>6</sup> have introduced crystals of estrogenic hormone subcutaneously. This has proved economical and effective by virtue of the slow absorption of the crystals, and the action of the estrogen has been greatly prolonged. It will be of interest to see whether such prolonged action on the endometrium will result in bleedings which cannot be well controlled. This has apparently occurred in 4 of 20 patients treated with



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implants by Twombly.<sup>7</sup> This problem does not exist in the absence of the uterus. The final choice will undoubtedly be the oral route once the cost of estrogens is lowered. One such estrogen, stilbestrol, which is very effective by mouth and is inexpensive, has been synthesized and has aroused great interest because of these properties.

Questions relating to dosage and the best methods for regulating therapy cannot as yet be answered with similar definiteness. Our relatively brief experience with estrogenic agents has not as yet permitted the recognition of the best principles on which to base a therapeutic regime. The wide variations from patient to patient in the subjective and biological response to estrogens make any attempt at standardization of dosage futile. There is likewise no general agreement as to the extent of symptomatic relief to be aimed at. An equal uncertainty exists as to which regime is best adapted to permit the hoped-for readjustment to the menopausal status.

The regime adopted in this Clinic may be briefly set forth with full appreciation of what may prove to be its shortcomings. It is based on the control of hormonal therapy by means of the vaginal smear rather than on subjective symptoms alone. Following a pelvic examination to rule out organic disease, and a psychological evaluation, the patient is placed on graded doses of an estrogen until a full follicular phase is reached. This represents complete replacement therapy. The first course of treatment extends over 4 to 5 weeks during which a correlation is made between the degree of smear change and the extent of subjective relief. This permits the observer to judge the sensitivity of the individual response to the estrogen, the level of dosage and the smear change at which optimal effects occur, and the character of the symptoms for which ovarian insufficiency is specifically responsible. One is frequently struck by the greater well-being which can be achieved in this way than when subjective indices such as the flush are relied upon exclusively. The results of this first course of therapy serve as a guide for further management.

Treatment is then interrupted. The speed and intensity with which symptoms recur enable one to form an opinion as to the severity of the syndrome and the probable ease or difficulty of the eventual readjustment. The second purpose of the rest period is to permit the regression of the induced endometrial hyperplasia in order to avoid the discomfort of bleeding from a too-prolonged uterine stimulation. Bleeding

will, however, occasionally occur and its significance should be made clear to the patient.

Treatment is resumed after a two-week interval if the return of symptoms warrants it. The dosage and level of the smear which afford optimal relief is now selected. Excessive dosage is thus avoided and the full benefit inherent in the therapy realized. The response of the patient to this regime is extremely variable. With favorable cases, each succeeding course finds optimal symptomatic relief achieved with progressively smaller doses until the need for further support ceases entirely. In the unfortunate, large doses may be required for many years with little or no evidence of an impending readjustment. All stages between these extremes are seen. Along with the hormonal therapy every effort is made to deal with other factors which may contribute to the persistence of symptoms. Of most value in this respect is the psychotherapeutic approach.

The problems involved in spacing the treatment deserve brief comment. Where oral administration is possible, it is most efficient to give the hormone daily. When the intramuscular route is employed the inconvenience of daily injections is usually an obstacle to the maintenance of an even concentration of hormone in the body. It can be shown by studies of the vaginal secretion that the more widely spaced the less efficient are injections of estrogens even if conjugated with benzoic or propionic acid. The practice of giving large doses of estrogen at long intervals is not only inefficient but carries with it whatever dangers may be inherent in the marked and repeated shifts in the histology of the endometrium change it induces. In the hysterectomized patient this difficulty does not exist but the possible effects on the breast must be borne in mind in relation to malignancy.

Concern has been expressed lest intensive estrogenic therapy delay the eventual readjustment. This has led many workers to recommend that the dose be just that which allows the patient to be comfortable and that it be steadily and systematically reduced with a view to assisting the readjustment of the post-menopausal status. This regime may prove satisfactory for some patients but for the most part I have been unsuccessful in accelerating readjustment by such an enforced reduction in dosage. It is my impression that estrogenic therapy per se does not interfere with the eventual transition and that there is little reason to withhold the full benefit inherent in these therapeutic agents.

This chapter would be incomplete without reference to the management of menopausal symptoms arising during the climacteric prior to cessation of menstruation.<sup>8</sup> These symptoms are occasionally as severe as those seen at the menopause. While they may occur throughout the cycle, they are more commonly present premenstrually and during the flow, disappearing with the increased estrin production of the developing ovarian follicle. They respond equally well to replacement therapy. When they occur premenstrually they are best treated by the administration of estrin from the mid-point of the cycle up to a few days before the expected flow. When they occur at menstruation the flow need be no contraindication to the administration of estrogen, in the absence of pelvic disease. Not infrequently it serves to reduce the excessive flow which may occur in the climacteric. The dose on the first and second day should be relatively small, for example, about 500 R.U., and may be raised on the succeeding days until the symptoms disappear. It is often helpful when symptoms occur during menstruation to administer the hormone for a short period premenstrually as well. When symptoms occur throughout the cycle, estrin should be administered throughout. As at the menopause, no standard dosage can be prescribed. The average patient experiences relief with 1,000-2,000 R.U. three times weekly except for a 3 to 4 day period prior to the expected flow, but here again each patient presents an individual problem.

### *The Synthetic Estrogen, Stilbestrol*

This interesting therapeutic agent, diethyl-stilbestrol, was synthesized by Dodds and his associates in 1938.<sup>9</sup> As may be seen from its formula, it differs from the natural estrogens in that it does not contain the phenanthrene-ring system formerly thought to be necessary for estrogenic activity.

It was found to be an extremely powerful estrogenic agent in animals, suffering little diminution in potency by the oral as compared to the parenteral route. It reproduced virtually all the effects of the natural estrogens in animals and was about two and one-half times as active as estrone by injection. By mouth, its superiority over the natural estrogens was even more striking. It will be recalled that the natural estrogens, estrone and estradiol, like the thyroid hormones, are effective by mouth. However, about 15 to 20 times the parenteral dose must be administered orally to produce the same effect, as judged by vaginal

smears. Stilbestrol, on the other hand, lost half or less of its activity by mouth. These attributes, its high estrogenic activity, its oral efficiency, and its cheapness, gave promise of a wide usefulness in human therapy. Preliminary experiments on animals had indicated that it was devoid of toxic activity.

The first reports of its clinical use were highly favorable.<sup>10,11</sup> Stilbestrol reproduced all the effects observed with the natural estrogens, including the relief of menopausal symptoms. More extensive clinical studies, while confirming its estrogenic properties and attendant relief of symptoms, brought out certain undesirable side reactions chiefly referred to the gastrointestinal tract, and consisting of nausea, vomiting and anorexia. Also evidence began to accumulate from toxicity studies that its use in animals was sometimes followed by damage to various tissues, especially the liver.

Our own experience with stilbestrol<sup>12</sup> was derived from a study of a series of forty-four women, two of whom had primary amenorrhea, in whom estrogenic activity was the chief point of interest, and forty-two with the menopausal syndrome, who permitted an evaluation of its effects on symptoms. The estrogenic effects were followed by vaginal smears and biopsies. The therapeutic goal in each patient was the induction of a full follicular smear as well as symptomatic relief. The results of our study may be briefly summarized as follows.

We could confirm the previous observations that stilbestrol is a powerful estrogenic agent losing little of its potency by mouth and capable of ameliorating subjective symptoms of the menopause. The oral estrogenic unit for the human was found to lie between 2 mg. and 4 mg. daily.

Its use, however, was associated in our series with a high percentage of toxic symptoms in the form of nausea, vomiting, abdominal distress, anorexia, diarrhea, lassitude, paresthesias, vertigo, thirst, and skin rashes. There appeared to be no relation between the size of the dose and the development of toxic reactions; nor was there evidence of an acquired tolerance to the drug. The side effects appeared to be largely central in origin since they followed injection as well as oral administration. Liver function tests were inconclusive.

The incidence of side effects in the group of patients studied was a good deal higher than other workers have reported. Their existence, however, whatever the incidence, certainly warrants caution in the use

of this preparation and our feeling is that, until the nature and significance of the toxic effects are understood, it should be regarded as an experimental preparation.

One is tempted to speculate on the nature of the toxic results obtained with stilbestrol. It is of interest that the two synthetic estrogens, stilbestrol and ethinyl estradiol, have this in common, that they are both very potent by mouth and both produce the same type of toxic side reaction. The explanation for the loss of potency of the natural estrogens by mouth is held to be their degradation during passage through the liver. This organ has been shown to have the capacity to destroy natural estrogens by some still obscure process. The synthetic estrogens apparently escape this degradation in the liver. At least such an explanation would account for their oral potency. Such a mechanism may function to prevent the accumulation of estrogens in the circulation above levels which are adequate for their effects on the structures they specifically influence. An excessive accumulation in the blood stream might have an unfavorable effect on other structures in the body. We may well be witnessing with stilbestrol those undesirable effects which are prevented with the natural estrogens by this mechanism of neutralization. The greater oral potency of stilbestrol may therefore be gained at the expense of the safety of the organism.

### *The Male Sex Hormone in the Menopause*

The history of the use of male hormones in disturbances of female sex physiology is an interesting one. The existence of both hormones side by side in both sexes still awaits a full explanation. Animal experiments in which the balance between estrogens and androgens has been altered artificially, have afforded some clues. The first effect observed was an inhibition of the pituitary with a subsequent suppression of the estrous cycle; the second was a neutralization of the peripheral effects of estrogens on the secondary sex structures. A similar type of action has also been found in man. Loeser<sup>13</sup> first demonstrated the atrophic effects of androgens on the endometrium in women and pointed out its use in dealing with excessive bleeding. Studies from this laboratory<sup>14</sup> showed that human menstruation could be suppressed at will with androgens, to return when treatment was stopped. We were also able to demonstrate a peripheral antagonism between the male and female sex hormones in the case of vaginal epithelium.<sup>15</sup> The ratio of

androgen to estrogen, necessary to produce this effect, was about 50 to 1. This is far greater than the excretion ratio of these hormones in women. Hence the estrogenic influence predominates. In man, therefore, the same types of effects were to be observed as in animals—an inhibitory effect on the pituitary with subsequent suppression of menstruation, and peripheral neutralization of estrogens by androgens.

What was quite unexpected was that androgens should be capable of abolishing the symptoms of the menopause, although one property was common to both types of hormones, i.e., the ability to depress the excretion of urinary gonadotropic hormones of pituitary origin.<sup>16</sup> That the androgens were indeed capable of ameliorating the symptoms of the menopause became apparent from the work of Salmon<sup>16</sup> and others as well as from our own studies.<sup>15</sup> The effective dose was rather high, in the neighborhood of 25 mg. daily. The use of androgens in the menopause had one advantage; it was unassociated with any withdrawal bleeding, since its effect on the endometrium is to induce atrophy rather than hyperplasia.

However, disadvantages soon became apparent in the form of increased hirsutism, enlargement of the clitoris, and a lowering of the voice, unpleasant sequelae which often take a long time to reverse themselves. When one considers the duration of replacement therapy in the menopause, it becomes apparent that this symptomatic effect of the androgenic hormone, while of interest to the student of sex physiology, does not justify its use as a substitute for the natural estrogens.

#### ESTROGENS AND CARCINOMA IN MAN

One of the deterrents to the widespread use of estrogens in man has been a consequence of animal experiments demonstrating the capacity of these hormones to produce carcinoma under certain conditions. It is not yet clear whether the carcinogenic effect of the estrogens is direct or dependent on the release of genetic predispositions on the part of these animals. Whatever the explanation, there has been considerable concern over the possible effects of the extensive use of these hormones on the incidence of carcinoma in the human.

Conditions under which carcinoma is produced in animals differ in certain important respects from those under which the estrogens are ordinarily used in human therapy. Carcinoma is most readily induced in strains of animals having a high incidence of spontaneous carcinoma.



The amount of estrogen administered has been very large in proportion to the weight of the animals. Furthermore, the hormones must be given over a large part of the life span of the animals.

In humans it is impossible to assay the innate tendencies towards carcinoma; the duration of therapy is relatively short and the dose of estrogens ordinarily employed is physiological, approximating the quantity elaborated in the normal economy of the organism.

This problem cannot be approached as directly in man as in animals, for one cannot deliberately seek to bring about the production of carcinoma in man except under unusual circumstances. We are, therefore, forced to evaluate the significance of estrogenic therapy in the human by analyzing the incidence of new growths in large series of cases in which the hormones were used for a sufficient length of time to make this evaluation significant. Other methods of approach take the form of studies of the histological changes in the uterus after prolonged therapy.<sup>17,18</sup>

We have analyzed a series of 452 cases treated with estrogens during the past seven years at the New York Hospital.<sup>19</sup> Most of these patients were treated by a similar regime, making them a relatively uniform group. Every precaution was taken to minimize factors which might predispose towards carcinogenesis. Prior to any treatment, thorough pelvic examinations were made and any inflammatory lesions found were corrected because of the relationship between chronic inflammation and carcinoma. Repeated gynecological check-ups of the state of the pelvis were made and the breasts carefully examined for the presence of nodules. The therapeutic use of the hormones was controlled by means of vaginal smears, permitting full replacement therapy to be achieved in most of the patients and the avoidance of excessive doses. No patient, therefore, received at one time more than would be equivalent to one human unit. This is far lower than the amounts needed to produce carcinoma in animal experiments. Thirdly, the estrogens were given with as short an interval as feasible between doses in order to avoid the irregularities of endometrial hyperplasia and regression which might be favorable conditions for neoplastic changes. In patients with an intact uterus, treatment was interrupted every four to six weeks to allow for a regression of the endometrial hyperplasia and to avoid a too prolonged stimulation.

An analysis of this group of 452 cases shows that at least in one

respect it fulfilled the conditions of the successful animal experiments, namely, a high tumor population. There were 82 cases of benign myomata of the uterus with removal prior to treatment, and one carcinoma of the fundus, also removed prior to treatment. Ninety-eight ovaries were removed, all benign; and there were nine mastectomies, three for malignant neoplasms. Of this group, one woman, who had a bilateral mastectomy in 1934 with the finding of an adenocarcinoma in one breast, developed metastatic lesions and a recurrence of the breast tumor four years after the original operation. She had received in this interval 3,000,000 I.U. of estrogen. The recurrence within this time does not warrant the conclusion that the estrogenic therapy was responsible. Otherwise the series was free of any instances of development of neoplasm. This, in conjunction with other studies cited, appears to offer no support for the view that the use of the estrogenic hormones in man is associated with the danger of neocarcinogenesis, provided therapy is carefully controlled in the manner indicated.

#### RESULTS FROM ESTROGENIC THERAPY IN THE MENOPAUSE

Since the signs and symptoms which present themselves at the menopausal age are part of a complex situation in which ovarian insufficiency is but one of the etiological factors, it becomes of importance to try to ascertain what effects may be expected from the use of hormones alone. In this way we obtain a better sense of proportion as to the significance of the whole set of changes at this life period. For those symptoms and signs which are not corrected by replacement therapy, other approaches must be sought or they must be accepted as inevitable consequences of the decreascent period of the life cycle.

The classical symptoms of the menopause, such as the vasomotor crises, headache, asthenia, insomnia, and the disturbances of peripheral circulation, may be expected to disappear at various levels of replacement therapy. Some of these, such as the hot flush, disappear more rapidly than others and are not too good subjective criteria on which to guide dosage. Pushing therapy to full replacement is the most certain method of determining the degree of well-being which can be experienced. No more gratifying restoration of health can be achieved in therapeutics than is so frequently seen in the menopause under adequate treatment.

Too much, however, must not be expected as regards many signs

and symptoms which accompany this syndrome but which are apparently part of a more fundamental alteration characteristic of this age period. One of the most troublesome complaints is that of joint pain involving particularly the knees, spine, and hands, and occasionally most of the other joints. It is an osteoarthritis of degenerative character, and seems to be specifically associated with the climacteric. Obesity tends to accentuate the difficulties. Hall<sup>20</sup> has reported considerable relief of these symptoms with estrogenic hormones. Our experience agrees with his in that, on the whole, the arthralgias are benefited. They may nevertheless persist, and frequently severely, despite intensive estrogenic therapy. They appear to belong to the group of degenerative changes in this age period the progress of which can be only partially influenced by ovarian hormone therapy.

There is some difference of opinion as to whether the hypertension so often seen at the menopause is specifically influenced by estrogenic therapy. Analysis of our results indicates that a well-stabilized hypertension is scarcely, or not at all, influenced by hormonal therapy. Where marked variations in blood pressure are encountered in association with emotional instability, the tension may be expected to be stabilized at the lower levels when estrogenic therapy has reduced the vasomotor instability and emotional tension. Nor does the obesity of this period seem to have any specific relation to the ovarian insufficiency. It should be dealt with by those measures which are employed at other ages, with, however, an avoidance of drastic procedures.

The anticipation that the estrogens would function as sex hormones in the sense that they would be able specifically to influence libido, has not been realized. There is a growing awareness that the sexual drive is grounded in more fundamental factors, and that the concept that it was solely dependent on the reproductive secretions was an oversimplification of an extremely complex and subtle reaction. The changes in libido at the menopause are inconstant and to a large extent dependent on the intensity of the previous sexual drive and on the general discomfort attendant on the menopausal syndrome. The most that should be expected from replacement therapy is that libido be restored to its premenopausal level. The few instances where libido is increased are attributable to non-hormonal influences which enter the complex picture of this age period.

The psychic disturbances so prominent at this age period present an

involved picture which make it necessary to discriminate in terms of the character of the disturbance. The ability of a woman to survive the menopause without serious emotional disturbance is an indication of her previous emotional stability. A large proportion of the women who seek relief from menopausal symptoms have been maladjusted for a long time prior to the onset of the menopause. The majority of these women have presented psychoneurotic symptoms of the neurasthenic and hypochondriacal type. With the additional stress of the menopause these symptoms become accentuated. In addition, there are likely to be symptoms of anxiety and tension.

If there has not been serious maladjustment of the psychoneurotic type, the menopausal symptoms such as the depression and emotional instability are rather promptly relieved by hormonal replacement therapy. On the other hand, if the psychoneurotic maladjustment has been marked, there is usually only partial relief or relief of a temporary character, and some form of psychotherapy is necessary.

A smaller group of patients have more deeply seated problems such as may be noted in introverted or schizoid personalities. These patients tend to develop chronic hypochondriacal complaints, and sometimes the clinical syndrome of involutional melancholia. It would appear that, in the involutional cases, the menopause acts as a factor in precipitating a psychotic reaction which had for some time been latent and which represents a combination of personality problems for which there is no apparent solution. Feelings of guilt because of tabooed sexual thoughts or practices, or the resentment over the realization that the sex life is in part terminated, impose a burden to which the woman is unable to adjust.

An optimistic view with respect to the therapeutic benefit of estrogenic therapy in the psychotic reactions of the menopause has been expressed by several groups of workers, particularly Werner and his associates,<sup>21</sup> who have reported very favorable results with estrogens in involutional melancholia. Our more pessimistic attitude is based on a study of a small series of cases carried out with Ripley and Papanicolaou<sup>22</sup> in the Payne-Whitney Clinic of the New York Hospital. Of these, twenty were intensively studied for long periods. Seven were instances of involutional melancholia, six fell into the manic-depressive group, seven were milder reactions of a more reactive nature which may be classified as psychoneuroses of the depressive type. Full replace-

ment therapy, controlled by vaginal smears, with far larger doses than those employed in the previous studies cited was given for long periods during hospitalization.

Our general conclusions were that no specific effect on the psychosis could be expected from estrogenic therapy. Wherever associated menopausal symptoms contributed to the discomfort of the patient, these symptoms could be abolished. With this improvement in the general well-being of the patient came a somewhat better ability to cope with their problems, but this aid was of a non-specific character.

#### PROBLEMS STILL PRESENTED BY THE MENOPAUSAL SYNDROME

Despite the gratifying progress that has been made in the treatment of the menopausal syndrome, many questions still remain unanswered. The situation is somewhat analogous to Graves' disease and diabetes mellitus where a therapeutic measure of considerable effectiveness still leaves unsolved many of the primary problems relating to the genesis of the disease.

Of the questions still awaiting solution, one may be singled out for brief comment in concluding this survey because of my growing conviction that it may reach to the heart of the problem. Our therapeutic successes should not cause us to lose sight of the fact that we have no knowledge of the cause of the menopausal syndrome. We believe that it represents a failure to adjust to the new internal environment which follows the cessation of ovarian function; but why this occurs in one group of women and not in the other remains obscure. When one studies the menopausal syndrome from the broader aspects of the evolution of the total personality, it becomes increasingly apparent that here as well as in Graves' disease, psychogenic factors may play a very important, if not primary, role in preventing an adjustment to the new status. One sees instances in which the adjustment to the menopause had taken place smoothly years before, and where acute and distressing symptoms suddenly arose years afterwards in association with some emotional stress. One sees relief of menopausal symptoms following therapy with an apparent satisfactory adjustment suddenly interrupted by a renewal of all the old complaints in their original intensity under the influence of some new psychic strain. The importance of psychic influence is also commonly seen in the greater resistance of the severely psychoneurotic menopausal patient not only to the subjective but to

the biological effects of estrogenic hormones.

The implications of these observations for the direction of our future approach to the study of the problem of the menopause are apparent. The sooner we learn to regard the menopausal syndrome not as an entity but as a symptom of a more fundamental psychobiological maladjustment, the more rapid will be the attainment of our eventual therapeutic goal, its prophylaxis.

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## CLINICAL ASPECTS OF RHEUMATIC FEVER IN CHILDREN\*

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IT WOULD be presumptuous on my part to recite the manifest symptoms which we associate with rheumatic infection in children. These are well known to all of you. It is a subject too vast to cover adequately in the short time allotted to me. Suffice it to say that this disease is a scourge of childhood, and takes a heavy toll in the first two decades of life. That the New York Heart Association should see fit to devote an entire evening to its consideration is significant and important. Rather, would I attempt to point out some of the minor patterns of rheumatism in children which are less frequently recognized. The alert physician should make at least a presumptive diagnosis in the subclinical phase of the disease, and should avail himself of the laboratory tests to supplement his clinical observation. The child who tires easily, who unaccountably is losing weight, has a poor appetite, is becoming more pale, and has indefinite muscle pains, should arouse the suspicions of the physician and a careful survey and appraisal should be made. Mild types of chorea may be overlooked, and the physician should be on the alert, in the knowledge that even mild chorea may induce carditis of a severe degree. A low grade fever may be discovered, and the erythrocytes may sediment more rapidly than normal. These are minor patterns of the disease in its early stages.

We too often err in thinking that rheumatism and joint infection are synonymous. Polyarthritis, associated with rheumatism, is not nearly as frequent in childhood as it is in later life. We should get away from this concept, and be more alert in the early recognition of the disease. I am more and more impressed with the absence of joint symptoms in many of these rheumatic children, particularly in the early years. McIntosh and Wood reported twenty-four children at the Babies Hospital who developed the disease before three years of age. Less than half

\* Read March 26, 1940 at The New York Academy of Medicine at the meeting of the New York Heart Association.



of these gave a history of having had joint symptoms. Ninety-six per cent exhibited either clinically or pathologically rheumatic heart disease. The youngest case was twenty months of age.

We hear much about "growing pains" in children. That these occur in the absence of rheumatic infection is unquestioned. The physician is often puzzled to differentiate the rheumatic from the non-rheumatic pains. It is here that laboratory aid must be sought. The observation of Hawksley in England and of Shapiro in this country at a meeting of the American Rheumatism Association would indicate that growing pains are not uncommon in healthy growing children, and that a very small per cent develop rheumatic carditis. An interesting explanation has been given by Erdheim, that in certain rapidly growing children, minute fractures of the metaphyseal plate occur. He has demonstrated these minute fractures at the growing ends of the long bones in children who have died of acute illness or by accident. This is, by far, the most satisfactory explanation of "growing pains" that I know. To my knowledge there has been no report of this in the English literature. On the other hand, we do see children suffering from severe carditis with no other history than that of "growing pains." The differential diagnosis should be made, or at least suspected, so that prompt treatment may be instituted. Where rheumatism is suspected, such laboratory aids as the electrocardiogram, the sedimentation rate, the white blood count, and the Addis count in the urine, may be helpful. I have had no experience with the Weltmann sero-coagulation reaction as a non-specific test. This needs to be further evaluated. At present the erythrocyte sedimentation rate is probably the most valuable single blood study in rheumatic infection. It needs no elaborate apparatus nor laborious technique. It is therefore important to differentiate "growing pains," not only from the standpoint of the child, but also in the study of the problems of rheumatism. Partial invalidism and institutional care may thus be prevented in a group of children who are erroneously diagnosed as having rheumatic infection.

Abdominal pain may occur in the rheumatic state, and may be so acute as to simulate other surgical conditions, notably appendicitis. Some years ago we reported an appendectomy performed on an eleven year old negro boy who, a few days later, with a persistence of the fever and a rapid sedimentation rate, developed polyarthritis, an erythema marginatum, and evidence of carditis. In this case the pathologist made

a presumptive diagnosis, and on his report asked, "any evidence of rheumatism?" The pain, in this case, was probably only partly due to the appendix. It is more than likely that the greater part of the pain was due to an invasion of the peritoneum, or a periarteritis involving the mesenteric vessels. It is well to note that abdominal pain may be a pattern in the rheumatic picture, and often will confuse the clinician in the determination of its cause. Obviously it is important to do so.

Over a period of eighteen years it has been my privilege to have had an opportunity to observe over long periods of time in three cardiac homes near New York a large group of children afflicted with rheumatic heart disease. We (I use the word "we" advisedly, for there have been many individuals concerned in this study, and without their arduous labors, loyalty and enthusiasm, this work could not have been possible) have cared for, under as ideal conditions as it is possible to attain in a convalescent home, some 1,378 children. Seventy-nine of these were drawn last year from some thirty-one cardiac clinics in the five Boroughs of New York City. This group of children, at the time of their admission to these Homes, by all the known criteria and laboratory tests, have been in the quiescent stage of their infection. However, even under ideal living conditions, reinfections do occur, and often necessitate a return of the child to the hospital from which he came. This is a discouraging feature of the work, but there are many encouraging ones; 962, or 70 per cent of these children are living, and the majority leading useful lives. One hundred and eleven have been married, and eighty-six children have been born of these marriages. Since children are accepted only when there is not a predominating throat culture for beta-hemolytic streptococci, recrudescences are less than was formerly the case. We find that these reactivations are preceded as a rule by an upper respiratory infection some two weeks prior to the onset. The child complains of a sore throat, and there is a sharp rise in fever which subsides in two or three days. This is Phase 1 of the 3 Phases which Coburn and Pauli have described in the evolution of rheumatic fever. Then follows Phase 2 of about two weeks, which is afebrile and symptom free. Then Phase 3 ensues. This is the period of acute rheumatic symptoms. Coburn and Pauli state that Phase 2, the afebrile stage, is "the crucial stage in the genesis of rheumatic symptoms." They have demonstrated in this Phase 2 a diminution in serum complement, which becomes further reduced during Phase 3. In commenting on their

work, the Journal of the American Medical Association says editorially that "since decreases in serum complement are known to take place when antigen and antibody coexist in the circulation, Coburn and Pauli postulate the existence of a Phase 2 pre-rheumatic antigen, reacting with a Phase 3 antibody as a cause of this complement 'deviation.' The demonstration of secondary antigens and antibodies in rheumatic fever is clinical confirmation of a speculative hypothesis proposed a decade or more ago by immunologists. If confirmed, this renaissance of the speculative theory of secondary anaphylaxis and immunity may lead to practical diagnostic and therapeutic methods in numerous infectious diseases."

What I want to point out is that these reactivations are unpredictable in any given child and are often bizarre in their manifestations. They often present no symptoms or signs except a low grade fever and accelerated heart action. The late Lucy Porter Sutton stressed so often gallop rhythm as an important sign of activity. In an institution these children with reactivity and active carditis may be discovered in their subclinical phase by laboratory aids, but one wonders how many are running the streets and even attending school with few if any symptoms, and yet in the active phase of the disease. You can thus see why it is so difficult to determine what constitutes a reactivity in the follow-up of these children, and what makes the whole problem of rheumatic infection such a prodigious one. Monocyclic types of rheumatic fever are not common in children. The questions arise: "What criteria can we apply to determine reactivation?"; "when does infection end and convalescence begin?"; "why does one child have but one bout of rheumatic fever and another (perhaps a brother or sister) have five or six bouts?" Added knowledge each year is helping to answer these perplexing questions.

As this meeting is planned to promote an educational campaign in the interests of rheumatic fever, a few words should be spoken about this disease as a public health problem. The morbidity and mortality figures of rheumatic heart disease are staggering. The incidence in this country is conservatively set at about 800,000 to 1,000,000 individuals, and the mortality about 40,000 deaths each year, with the average age at death, thirty years. Until rheumatic fever is made a reportable disease we will have no accurate data. Why the Public Health Services and Departments of Health have not seen fit to do this is hard to under-

stand. The incidence of rheumatic valvular lesions in children is about 1 per cent of the school population. This would mean that about 10,000 school children in New York City are so afflicted. As they grow up these make up the greater number of adult cardiacs in the second and third decades.

But the morbidity of rheumatic heart disease is overshadowed by the high mortality. Our figures indicate a mortality rate of 30 per cent in the group of 1,378 children followed for 18 years, that is 416 deaths. This has risen from a figure of 28.7 per cent in 1938. We have found that over half of these 416 deaths have occurred within the first five years of their initial infection. This coincides with Duckett Jones' observation of 1,000 children with rheumatic carditis. Two-thirds of those dying have died within 5 years of their primary infection. Duckett Jones' 10-year follow-up on 1,000 rheumatics shows a 25 per cent mortality. Stroud's recent 15-year follow-up on 685 children reports a mortality rate of 21 per cent. Death is not common in the first attack, but occurs more often in the second or third attack. From this it is quite obvious that the most important time in the life of the rheumatic child is the first five or six years following the initial infection. This occurs usually between five and twelve years of age, the average age being seven years. The brunt of our attack on this dread foe of childhood then must be during these all important years following the primary invasion. It is well to interpolate here that most of these children die of their infection and not of congestive heart failure, as is more common in the young adult cardiac.

From what we know concerning the devastating effects of rheumatic fever is it not evident that this disease has become a public health problem of major importance? It becomes our concern. In the first place, in our own State of New York, the term "cripple" should be broadened so as to include the child with rheumatic heart disease. Howard Haggard of Yale University has coined the phrase "Crippled children who do not limp." The American Academy of Pediatrics has put itself on record in the cause of children so crippled with rheumatic carditis. It is difficult for the lay person to visualize a child with a damaged heart as a cripple or as handicapped. The boy or girl may not look ill, but in spite of this, his or her activity may be greatly curtailed, and the games and sports of normal children denied. Too often the span of life is shortened. Our figures show that 363 or 87.7 per cent of the

total 416 deaths have occurred before the age of 20 years. The orthopedic cripple, or the child crippled by infantile paralysis, arouses our sympathy, and justly so, but when one considers that rheumatism destroys seven times as many children as does anterior poliomyelitis, then you have some conception of the ravages of the disease. In one sense, the child stricken with infantile paralysis is more fortunate than the child stricken with rheumatism. The latter confers little if any immunity, and reactivations occur all too frequently. In fact they are more often the rule than the exception. Each one adds still further injury to a heart already damaged. On the other hand, infantile paralysis, as dread a disease as it is, usually confers an immunity to subsequent attacks and the afflicted child may anticipate varying degrees of return of function. To quote from a recent article, "a child with a withered leg can see his own infirmity, and seeing it, understand it. A child with a crippled heart cannot see his injury; he must be told, and, having been told, believe it. He must suit his life to an intangible infirmity that imposes its limitations on all of his physical activities."

Many children who contract infantile paralysis recover completely with no resultant paralyses or crippling. Very few children who contract rheumatism escape without some damage to the heart of greater or less degree.

It is my hope that an educational campaign in the cause of rheumatism may be extended and organized on a par with the infantile paralysis, tuberculosis and cancer campaigns. From the standpoints of total mortality and age at death it ranks as one of our major health problems. At this time, when the Children's Bureau in Washington has embarked on a program for the care of the child crippled with rheumatic heart disease, it would seem that "now is the accepted time" to mobilize all individuals and health agencies interested in this problem. I hope that this meeting tonight, and the annual meeting of the New York Tuberculosis and Health Association just three weeks ago, to which the New York Heart Association contributed, may provide the stimulus to initiate such a campaign of education in the interests of these crippled children, adolescents and young adults. The President, speaking on the scourge of infantile paralysis a few weeks ago, said: "As the years go on, I hope that the task will be extended to care for all crippled children, no matter what the cause of their crippling."

There is an urgent need for more beds, first, for sanitorial care,

comparable with London's 1,100 beds, and, second, for the convalescent child in the quiescent stage of the disease. Only 500 beds for convalescent care are available in this country, of which nearly 300 are in the vicinity of New York City. Such a provision would allow for prolonged bed rest which is so necessary. Long bed rest would seem just as advisable in this disease as in tuberculosis. It is well to note that about 66 per cent of these children are discharged from the acute hospital after an average of only one month's care; and the majority return to homes of poverty, want and bad hygienic surroundings. Is it any wonder that reactivations occur, and that so many succumb to their infection?

I cannot end this paper without a word concerning the larger problem of the child who is crippled with rheumatic heart disease. We must not forget that there is not only the heart to be treated, but there is also the child who has the heart. In other words, attention to the *psyche* is quite as important as attention to the *soma*, and may be even more so. There should be an integration of this psychosomatic relationship. The physician should have an awareness of the child as a whole, and should realize that the handicapped child has a greater need for help and adjustment than the normal child. Psychiatric counsel should be sought and should implement the therapeutic approach to the child with rheumatic heart disease. There are educational, social and emotional factors in the life of these children which require, often, the help of one trained in child psychiatry. This is an area in the care of the cardiac child which has been woefully neglected. It is an aspect which was stressed at the two-day conference on Convalescence last fall held in this building.

Too many children labelled cardiacs are being carried in clinics or taken care of by private physicians without justification. They are condemned to a life of partial invalidism merely because of a cardiac murmur. This is indefensible. How easy it is to develop an "invalid reaction" which later may become a neurosis, with feelings of insecurity, inferiority and anxiety. In my opinion, one of the most important functions of the cardiac clinic is to weed out these children who are stamped as cardiacs, but who have no organic disease of the heart. In doubtful cases I would prefer to take a chance with certain of these children rather than subject them to a life of partial invalidism with its train of psychic maladjustments.

I wish there were time to speak of the social service, and the vital role which the trained social worker plays in the total care of these

children. She is an important link in their guidance and rehabilitation. I know of no more important social work than this.

In conclusion, to those of you who were not fortunate enough to hear the John Wyckoff Memorial Lectures given by Dr. Swift a short time ago, I would commend them for your reading and study. They constitute the most thorough exposition on rheumatic fever that I know of. They will fill in the many gaps of this presentation.

## PURPOSES, FUNCTION AND USE OF STANDARD CLASSIFIED NOMENCLATURE OF DISEASE\*

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THE Standard Classified Nomenclature of Disease is now employed in almost all important hospitals and medical schools of the United States and Canada. Several years ago I found it in use in many of the large hospitals of London. At the meeting of the International Commission held in Paris in October 1938 for the purpose of preparing the decennial revision of the International List of the Causes of Death, it was the only reference work which the British delegation brought into the conference room as their standard authority on medical nomenclature.

The success of this American enterprise is largely due to the manner in which it was prepared during the years preceding the publication of the first edition (1928-1933). It was initiated and carried through to completion by a nationwide collaboration of all the important national societies representing medicine, surgery and the various specialties. It is to the credit of The New York Academy of Medicine that the Academy issued the first call to the conference of national societies just twelve years ago. When the national conference on Nomenclature of Disease was organized in response to this call, the Academy withdrew officially from participation, because as a local organization it had no place in a national body, if the nomenclature to be created was to be acceptable as authoritative throughout the United States and Canada. However, it continued to aid in obtaining the necessary financial support from various philanthropic foundations and insurance companies and provided office space for seven years.

Previously, there had been hundreds of local efforts, the best known being the Bellevue, the Massachusetts General, the Presbyterian, the Ponton, some named after hospitals, others after their authors. Increasing numbers led to increasing perplexity on the part of hospital administrators and clinicians. As they multiplied in number and variety, their

\* Read March 1, 1940 before the National Conference on Medical Nomenclature of The American Medical Association, Chicago.



many authors failed to appreciate the fact that they were modifications of preëxisting efforts which merely perpetrated illogical and overlapping methods of classification; that each was colored by peculiarly local hospital needs; and that in their separate parts they did not express the ideas or meet the demands of advanced experts in the highly specialized branches of medicine and surgery.

The purpose of a nomenclature is to encourage the use of expressive terms, the meaning of which can be accepted universally without ambiguity. The best term is the one which most completely expresses the nature of the disease. The names of discoverers of disease are generally unsatisfactory synonyms, are often the subject of dispute in various countries and sometimes even in different sections of the same country. Although Latin may be permissible for the generic classification of bacteria, the descriptive terms employed for the diseases should be expressed in English. As in the Middle Ages, Latin still serves to obscure the true depths of ignorance. This form of medical obscurantism lingers on in some of the more backward fields of medicine.

The primary purpose of a *classified* nomenclature is to arrange the diseases in a logical and orderly manner so that there may be no possibility of overlapping one another. This is important for accurate keeping of records in the disease file of a hospital record room. Now that almost all important hospitals use the Standard Classified Nomenclature, the disease files of their record rooms are mutually interchangeable. Their clinical experiences are readily available for study as well as for comparison with the experiences of other institutions.

The chief virtue of the Standard Classified Nomenclature of Disease is that from beginning to end it never departs from the simple construction of its basic schema. Every disease is described and classified topographically, in terms of the tissue or organ where it is principally manifested, and also into etiological categories. This has permitted the use of a simple library decimal system which greatly facilitates record room filing. The numerical designations on each side of the dash, often describe topography and etiology more accurately than the traditional name of the disease.

There has been some complaint that the six or more numbers necessary to designate a disease or injury do not lend themselves as readily for punch card recording as some simpler numerical systems. It must be remembered that the primary purpose of the Standard Nomenclature is

for clinical use. It is to encourage uniformity and accuracy in clinical expression. Our dual decimal system for the numerical designation of the diseases permits the employment of the Standard Classified Nomenclature of Disease as a clinical discipline, not only for fourth year medical students who as clinical clerks are being taught to think and to express themselves accurately and completely, but also often as a much needed clinical discipline for the attending staff of the hospital. Rebel at first, as they will, they soon learn to write their diagnoses in completely descriptive terms which can be filed by the record room clerk. "Contracted kidney" is not an acceptable term and cannot be filed unless the clinician describes the condition more completely as chronic glomerulonephritis, pyelonephritis, arteriolar nephrosclerosis, hydronephrosis, or congenital hypoplasia. If the clinician cannot make a complete diagnosis, that fact can also be recorded accurately. The record room must invariably know the complete diagnosis if it is available. If the clinician is dealing with a case of acute bacterial endocarditis or a case of poisoning, he must name the bacterium or the poison before the diagnosis can be filed or else he must state specifically that the cause was not determined.

In order to encourage the use of the Standard Nomenclature, many hospitals have purchased a copy for every ward and have chained the volume to each ward desk so that it is always available to the clinician when he is inscribing the final diagnosis on the patient's discharge card or on the clinical record.

The resistance of clinicians to making the little extra effort required by the use of the Standard Nomenclature is soon replaced by appreciation of an orderly disease file in the hospital record room. Medical students who have been subjected in the fourth year to the discipline of the Standard Nomenclature make better interns. We have reason to hope that the coming generation of practicing physicians who have come under its influence as students and interns will have developed the habit of thinking and speaking in more concise medical terms. No one will appreciate this more, I am sure, than the overburdened editor of the Journal of the American Medical Association.

Perhaps this was one of the reasons why I found no resistance on the part of Dr. Fishbein and the trustees of the American Medical Association when in 1937 on behalf of the National Conference I proposed to turn over to the Association the permanent responsibility for

the Nomenclature. This responsibility belongs rightly in the American Medical Association but in effecting the transfer, the hope was expressed at the time that the Association would continue to work through the medium of a National Conference, composed of all the national clinical societies, the Federal medical services and other interested organizations. By this nationwide collaboration the Standard Classified Nomenclature of Disease will continue to serve all the physicians and hospitals of the country as their authoritative guide on matters of diagnostic terminology.

Suggestions continue to be advanced that the Standard Classified Nomenclature of Disease is too large. We have given much thought to this matter of size. Physicians, whether in small or large hospitals, expect to find every disease term in a reference work of this nature. A significant abbreviation of the book can only be accomplished by omitting thousands of diseases of rarer occurrence and the volume would then lose its value even for small hospitals. The size of the volume and the number of terms it contains does not complicate the problems of the record room clerk or of the hospital physicians. In fact, the completeness of the nomenclature simplifies their work, for in the index or in the text they will find every known disease and in the basic schema there is a place reserved for every disease that is still unknown. The size and complexity of the disease file of a record room is not determined by the size of the Standard Nomenclature. In institutions, large or small, the disease file will only contain a record of those diseases which have been encountered in the hospital's own clinical experience.

As has been suggested by Dr. Edwin P. Jordan, the number of pages in the volume may be reduced by omitting certain common conditions which recur frequently in many parts of the body, such as abscess. The physician can combine the term "abscess" with any tissue or organ of the body and he or the record room clerk can then find the appropriate topographical code number by consulting the classification schema (pp. 17 to 58) and adding the etiological numerical designation for abscess and for the infecting agent. It would still be necessary to include some of the more common forms of abscess in the text, such as subphrenic abscess, abscess of the lung.

Surprising though it may seem, there are some who think the Standard Nomenclature is not large enough and who demand an opportunity to record various clinical manifestations of disease or even laboratory

findings. This is beyond the scope of a nomenclature of disease. No two institutions and no two men in the same institution can agree upon which symptoms of disease and which laboratory findings are worth recording in a disease file, and the same physician often changes his own opinion from year to year. Symptoms and laboratory findings are included in the complete clinical record of each case, and every clinical research requires a restudy of all the clinical records. To attempt to record such data in the disease file by means of supplementary code numbers is an unnecessary complication. Furthermore, it is usually inaccurate and undependable because of inconsistencies on the part of the clinical staff. Whenever an authoritative national specialist society such as the American Heart Association or the American Neurological Association has agreed officially upon the desirability of recording such specialized information under a supplementary system of coding, the list has been included in the volume.

A criticism of the Nomenclature is that it does not lend itself readily to cross reference to the rubrics of the International List of the Causes of Death. After each disease, the appropriate code number of the international list is to be found. This can be transferred to punch cards for statistical tabulation. In this manner morbidity can be compared statistically with mortality information.

Another criticism is that the Standard Nomenclature cannot conveniently be used for the statistical tabulation of summary reports on hospital morbidity. It must be remembered that the Nomenclature is designed primarily for clinicians, for the diagnoses as they make them are the sources of information concerning the prevalence and distribution of disease.

If group tabulations are desired, an abbreviated tabular list must be adopted for duplicate recording on punch cards. The tabular list may follow the disease arrangement of the international list of the causes of death so as to facilitate comparison of morbidity with mortality information. This was done successfully in the recent WPA study of the diagnoses of patients discharged from New York City hospitals. The difficulty in agreeing upon a tabular list for simplified statistical recording is that the information which is to be summarized statistically must differ radically if it is designed for hospital administrative purposes or for public health work. Such abbreviated statistical summaries seldom have any value for clinicians. A clinician is better served by

obtaining the specific information which he may desire directly from a complete hospital disease file which is properly classified for clinical purposes in accordance with the Standard Nomenclature.

Although this third edition of the Standard Classified Nomenclature of Disease may not require revision for five years, a central staff must continue to be maintained as the clearing house for the exchange of opinions on the use and the significance of both new and old diagnostic terms. Although the editorial influence of the Journal of the American Medical Association has long set a standard for the United States, the services which the assistant editor, Dr. Jordan, has rendered to the hospitals and the clinicians of the country in hundreds of details must be continued if nationwide collaboration is to be maintained.

## THE ADAPTATION OF THE STANDARD CLASSIFIED NOMENCLATURE OF DISEASE TO HOSPITAL MORBIDITY REPORTS\*

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HOSPITAL-SICKNESS experience is of interest not only to the medical and administrative personnel of each particular institution, but also to the community at large. Whether it be for the particular purpose of a single institution or from the broader community viewpoint, it is the mass aspect of the material rather than the minutiae that is of importance. It is the mass aspect of the statistical approach that gives it validity, in contradistinction to the minutiae of each particular case which are the *sine qua non* of the individual clinical study. It is only from the study of bulk phenomena that certain tendencies or perspectives become discernible. Among the important deductions from the study by W. J. Mayo<sup>1</sup> of 10,280 operations performed at St. Mary's Hospital, Rochester, Minn., was the statement that "some deaths and many poor end results occur with a regularity so definite that their incidence can be foretold from year to year." Only individual case studies can prevent the recurrence of particular untoward events. Many years ago, Frederick L. Hoffman<sup>2</sup> of the Prudential Life Insurance Company, in a special monograph, outlined the many significant facts which can be obtained from hospital experience. This study was based on the statistical data of Johns Hopkins Hospital from 1892 to 1911.

The experience of a single hospital gains much in significance when compared with that of other similar institutions. To make such comparisons valid there must be some agreement between hospital authorities as to common fundamental categories and as to terms. From the outset it should be recognized that mass statistics of hospital experience are of no clinical value or, at best, very limited clinical value; that scientific statistical studies of selected clinical conditions have no place in a hospital report and are beyond the scope of morbidity statistics.

\* Read March 1, 1940 at the National Conference on Medical Nomenclature, Chicago.

The compass of this paper precludes a detailed discussion of the value of morbidity statistics in general and of those of the hospitals in particular. This has been covered extensively in many other writings. The need of a systematic collection of morbidity data from various sources has, I believe, been well established.<sup>3</sup> Granted that such body of information is needed for civic, biosocial, pathometric, demographic, and actuarial purposes, the question is how should such a body of information be obtained and systematized and what part hospital experience should play in it.

For the moment, it is the latter or the hospital experience that is of particular moment and that only in its nosological relationships. Because, however, of the extensive use that has been made of mortality statistics in the discussions of incidence of disease, it may not be amiss to emphasize that death statistics, even when they are based on accurate certifications, give only a partial account of illness, for in the published tabulations only the principal or final cause of death is recorded and the contributory causes are omitted. These contributory conditions are often of socially greater importance than the terminal cause. Furthermore, to base the knowledge of the prevalence of illness on mortality bills, is often misleading. Ratios between morbidity and mortality in each disease are never constant. These ratios change not only with the varying virulence of the causative organism, if the disease is of germ or virus etiology, but also with the age distribution of the population of a given community, the economic environment and the existence or non-existence of medical institutions and their adequacy or inadequacy. Hence, generalizing with regard to morbidity on the basis of mortality is hazardous and may be utterly misleading.

In the foregoing paragraphs an attempt has been made to emphasize the need for hospital morbidity statistics apart from mortality statistics, and to indicate that such statistics are of service to the hospitals themselves and to the community at large. Now, as to the *modus operandi*. The experience of the Peter Bent Brigham Hospital, the Mayo Clinic, the Johns Hopkins Hospital, and some other individual efforts, is no doubt of much value. So also is the experience of three attempts in New York City at collective gathering of hospital data. Other communities may likewise have attempted the pooling of hospital morbidity data; in that event the base of experience is still broader. The first demonstration of the kind was made in New York under the direction of the Hospital Information and Service Bureau of the United Hospital Fund in 1923 in

coöperation with six hospitals.<sup>4</sup> In this experiment the simple method suggested by Bolduan<sup>5</sup> was followed. The participating hospitals agreed to send certain information concerning their discharged patients, using a form of certificate agreed upon, and these certificates were edited by a medical registrar in the same way as death certificates are registered by a registrar of vital statistics. There was no uniformity in the manner in which diagnoses or other data were reported from the coöperating hospitals. The second study on a much larger scale was that undertaken under a large WPA grant by the Research Division of the Welfare Council of New York City. It covered the entire annual experience of 113 hospitals in 1933 and comprised data pertaining to approximately 576,000 patients.\* Here again there was no uniformity in the reported facts and, as in the former study, a method of procedure had to be worked out to make possible a practical approach to the problem of classification. One of the valuable results of this experiment is the "Classified List of Diagnoses for Hospital Morbidity Reporting"<sup>6</sup> published by the Welfare Council of New York City. This is based roughly upon the Standard Classified Nomenclature of Disease, although the arrangement of the group diagnoses followed the International List of Causes of Death as far as possible. The third experiment is that which has been carried on for the last ten years by the Division of Medical Records and Statistics of the Department of Hospitals since 1929, when all the municipal hospitals in the City were consolidated into one department. The work of that Division under Caroline Martin is no doubt the most outstanding contribution in the field of hospital morbidity statistics, due to the remarkable ingenuity and competence of its direction and because of the insignificant cost of the enterprise.

Only recently has the Standard Classified Nomenclature been introduced in all the municipal hospitals and this has, no doubt, simplified the task of the central statistical office. Irrespective of the number of group classifications into which an abridged list must be divided, it is easier to use the individual entries of the Standard Classified Nomenclature than those of any other list, first because they are precise, and second because the scientific system of nosology developed in the Standard list has gained widespread approval and will no doubt become universal in time. If it should be advantageous to correlate the groupings of combined entries with the International List of Causes of Death, a method of cross-

\* This study has not been published as yet, except for a monograph describing the method used.



reference can be worked out which will serve the purpose. It is to be regretted that the Mayo Clinic Tabular Outline has been based entirely on the International Causes of Death, with such additions as were considered of importance from a pathometric or biosocial viewpoint.<sup>7</sup> Some of the items in that list could be omitted with benefit. There is no need in a hospital morbidity list of special entries for torticollis or for menopause or cretinism or idiocy and many other conditions rarely encountered in general hospitals. Whenever possible, the use of eponyms in any list should be discouraged on general principles. The Welfare Council list, though much shorter than that of Mayo Clinic, provides entries for numerically important conditions which are lumped in the Mayo Clinic outline, such for example as detachment of retina, strabismus, ulcer of the cornea, and other diseases of the ophthalmic system. On the other hand, the shortcoming of the Welfare Council grouping lies in the fact that it follows neither the International List nor the Standard Classified Nomenclature. Only five of the groupings in that list are based on the principle of etiology; the others refer to symptomatology or anatomical site. This may have been due to the need for tabulating poorly recorded information. Until the Standard Classified Nomenclature becomes generally used, a compromise arrangement may have to be used. It should, however, be pragmatically useful and should be generally agreed upon, as otherwise no valid comparisons are possible.

The four considerations followed in the tabulation of the material by the Welfare Council of New York City should be critically reviewed and such changes suggested as may be most acceptable for general adoption. The four guiding principles in the arrangement of the material in the Welfare Council classification were:

1. Elimination of superfluous diagnostic notations. In the actual tabulation of the 576,000 hospital discharge records, a single diagnosis was chosen for 78 per cent of the cases, two diagnoses were entered in 17 per cent, three diagnoses in 4 per cent, and in only 1 per cent of the cases were four diagnoses tabulated.

2. The discarding of complicating conditions which accompany the major condition or of typically secondary conditions.

3. The placement of several manifestations of the same etiology under one diagnostic designation.

4. Elimination of accessory conditions which are accidental and have no relation to the disease for which the patient was hospitalized.<sup>8</sup>

Neither the Mayo Clinic nor the Welfare Council classification lists surgical operations. From an administrative as well as a social viewpoint it is desirable that hospital reports include a classification of operations, prepared in accordance with some uniform, agreed upon method. The one used by the Division of Records and Statistics in the Department of Hospitals of New York City has proved of practical usefulness.

There are numerous other tabulations of administrative value which should be prepared and correlated with the medical and surgical experience of the hospitals, such as: total days' stay; mortality, although this is always of questionable value; occupations; and seasonal cycle. These and other important items do not come perhaps within the purport of discussion of this particular conference. I wish, therefore, to conclude with emphasis on several points in relation to hospital morbidity statistics:

First, the value of such statistics to hospital administration, to demography, to community planning, and to social insurance.

Second, the desirability of a uniform classification of hospital morbidity and of surgical operations for comparative purposes.

Third, the recognition of the fact that mass hospital statistics are of limited value from a clinical viewpoint, and that they are scientific only when they are carefully prepared and correlated in accordance with certain agreed upon principles of sound statistical procedure.

Fourth, the availability of the Standard Classified Nomenclature is a factor in making such tabulations easily referable to accurate clinical entries and simplifies the work of coding.

Fifth, hospital morbidity statistics should be prepared in close conformity with the International List of Causes of Death, because of convenience and cross-reference.

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## PROCEEDINGS OF ACADEMY MEETINGS

### STATED MEETINGS

MAY 2—*The New York Academy of Medicine*. Executive Session—a] Reading of the minutes; b] Presentation of certificates of fellowship. † Papers of the evening—Problems of aging—a] The general problem, George Morris Piersol, Professor of Medicine and Vice Dean for Medicine, University of Pennsylvania, Graduate School of Medicine;

b] Cardiovascular, Ernst P. Boas, Assistant Clinical Professor of Medicine, College of Physicians and Surgeons, Columbia University; c] Neuropsychiatric, Foster Kennedy, Professor of Clinical Neurology, Cornell University Medical College. † Report on election of Fellows.

MAY 16—*The Harvey Society* (in affiliation with *The New York Academy of Medi-*

cine) The Eighth Harvey Lecture, "The Chemical Composition of the Lipoids of the Tubercle Bacillus," R. J. Anderson, Professor of Chemistry, Yale University.

### SECTION MEETINGS

**MAY 3—Section of Surgery.** Executive session—a] Reading of the minutes; b] Election of Section Officers and member of Advisory Committee—for Chairman, Grant P. Pennoyer; for Secretary, Frank Brown Berry; for member of Advisory Committee, J. William Hinton. ¶ Presentation of cases—a] Tetanus following acute suppurative appendicitis with recovery, R. Sterling Mueller. Discussion, Seward Erdman; b] Mesenteric thrombosis with resection of small bowel. Result after two years. Traumatic rupture of the retroperitoneal portion of the duodenum, Caldwell B. Esselstyn. Discussion, Leon Ginzburg; c] Cases of subphrenic abscess illustrating paper of the evening, Abraham Jacob Beller. ¶ Papers of the evening—  
a] Subphrenic abscess with report of five cases, Abraham Jacob Beller. Discussion, John H. Garlock; b] Drainage of pelvic abscess through the rectal wall, Howard A. Patterson. Discussion, Paul C. Morton; c] Appendiceal abscess. Management and review of 100 cases, Edward Victor Denneen. Discussion, Charles Gordon Heyd. ¶ General discussion.

**MAY 7—Section of Dermatology and Syphilology.** Executive session—a] Reading of the minutes; b] Election of Section Officers and member of Advisory Committee—for Chairman, George C. Andrews; for Secretary, Herman Sharlit; for member of Advisory Committee, Louis Chargin. ¶ Presentation of cases—  
a] Cases from hospitals of Brooklyn; b] Beth Israel Hospital; c] Sea View Hospital; d] Miscellaneous cases. ¶ General discussion.

**MAY 7—Combined Meeting New York Neurological Society and Section of**

**Neurology and Psychiatry.** Executive session—Section of Neurology, Psychiatry. Election of Section Officers and member of Advisory Committee—for Chairman, Samuel Brock; for Secretary, George H. Hyslop; for member of Advisory Committee, Lewis D. Stevenson. ¶ Papers of the evening—a] Periodic dullness as an epileptic equivalent, H. H. Merritt (Boston), (by invitation), Tracy J. Putnam. Discussion, Richard M. Brickner; b] Electro-encephalographic localization of focal cerebral lesions, Herbert Jasper, D.Sc. (Montreal), (by invitation). Discussion, Leo M. Davidoff; c] The repetitive core of neurosis, Lawrence S. Kubie. Discussion, Bertram D. Lewin.

**MAY 8—Section of Historical and Cultural Medicine.** Executive session—a] Reading of the minutes; b] Election of Section Officers and member of Advisory Committee — for Chairman, Ramsay Spillman; for Secretary, Claude E. Heaton; for member of Advisory Committee, Louis Casamajor. ¶ Papers of the evening—a] Giuseppe Zambecari—a Seventeenth-Century Pioneer in experimental surgery, Saul Jarcho (by invitation). Discussion, Allen O. Whipple; b] Treatment of mental disorders in France at the end of the Eighteenth Century, C. P. Oberndorf. Discussion, A. A. Brill, Leland E. Hinsie.

**MAY 9—Section of Pediatrics.** Case demonstrations from 7:30 to 8:00 o'clock. ¶ Executive Session. Election of Section Officers and member of Advisory Committee—for Chairman, Leslie O. Ashton; for Secretary, Alfred G. Langmann; for member of Advisory Committee, Rustin McIntosh. ¶ Presentation of case reports—a] Roosevelt Hospital—Spherocytic jaundice with splenectomy in a five-months' old infant, Alexander T. Martin and James E. Thompson; b] Lenox Hill Hospital—A case of essential hypertension and precocious puberty, Irwin Philip Sobel; c] New York Post-Graduate Hospital—A case of Ehler-Danlos syndrome, George E. Pittinos

(by invitation); d] St. Luke's Hospital—Osteogenesis imperfecta—Lobstein type, Elizabeth B. Hinckley (by invitation); e] Polyclinic Hospital—Encephalitis following smallpox vaccination, Benjamin Roman (by invitation); f] Willard Parker Hospital—Guillain-Barre syndrome, Samuel Spector (by invitation); g] The Mount Sinai Hospital—Lymphocytic meningitis (2 cases), H. Kaufman (by invitation); h] Harlem Hospital—A case of scurvy with interesting roentgenograms, Harry J. Cohen (by invitation); j] Knickerbocker Hospital—Pneumonia in twins: Type I pneumococcus pneumonia involving identical lobes in identical twins, Lewis Jacobs (by invitation).

MAY 15—*Section of Otolaryngology*. Executive session—a] Reading of the minutes; b] Election of Section Officers and member of Advisory Committee—for Chairman, James W. Babcock; for Secretary, Page Northington; for member of Advisory Committee, Jacob L. Maybaum. ¶ Case reports—a] Otitic tetanus, Samuel Rosen; b] Thrombophlebitis of the cavernous sinus of otitic origin, Joseph G. Druss. ¶ Papers of the evening—a] The "blocked ear" of the caisson worker, Ralph Almour; b] Atypical facial neuralgia, George H. Hyslop. Discussion, Richard M. Brickner; c] Injuries of the larynx, traumatic and therapeutic, John D. Kernan. Discussion, Charles J. Imperatori.

MAY 17—*Section of Orthopedic Surgery*. Executive session—a] Reading of the minutes; b] Election of Section Officers and member of Advisory Committee—for Chairman, Lewis Clark Wagner; for Secretary, Joseph Buchman; for member of Advisory Committee, David M. Bosworth. ¶ Presentation of case. Loss of substance of the intervertebral disc following a spinal tap, John P. Stump. ¶ Papers of the evening—a] Posterior herniation of nucleus pulposus, Joseph S. Barr, Boston (by invitation). Discussion, Irving H. Pardee; b] Treatment of osteogenic sarcoma without

early amputation, Albert Ferguson (by invitation). Discussion, Ralph E. Herendeen. ¶ General discussion.

MAY 20—*Section of Ophthalmology*. Executive session. Election of Section Officers and member of Advisory Committee—for Chairman, Algernon Reese; for Secretary, Brittain F. Payne; for member of Advisory Committee, David H. Webster. ¶ Presentation of single case reports—a] Necrosis of the cornea due to vitamin A deficiency, Herman K. Goldberg (by invitation); b] Traumatic retinal angiopathy, James W. Smith; c] Recurrent advanced carcinoma of the orbit and nose; electrocoagulation and plastic reconstruction, Tibor de Chohnoky; d] Streptothricosis of the lacrimal canaliculi, Alfred Johnston Elliot (by invitation); e] Congenital ptosis—Machek operation, Rudolf Aebli; f] Molluscum contagiosum of lid margin as a cause of follicular conjunctivitis, Phillips Thygeson; g] Traumatic cataract affecting anterior layer of congenital nucleus, G. Bonaccolto; h] Sarcoma of the choroid. Probing of the lacrimal canal with negative pole, Walter Hipp; j] Birth injury of cornea with "glass membrane" in anterior membrane, Charles A. Perera.

MAY 21—*Section of Medicine*. Executive session—a] Reading of the minutes; b] Election of Section Officers and member of Advisory Committee—for Chairman, Oswald R. Jones; for Secretary, Asa L. Lincoln; for member of Advisory Committee, Samuel W. Lambert, Jr. ¶ Presentation of cases—a] Subacute Streptococcus viridans end-arteritis complicating patent ductus arteriosus. Recovery following operation, Philip Rosen (by invitation). Discussion, Arthur S. W. Touroff; b] Hypercalcemia of undetermined origin, Hector Perrone (by invitation). Discussion, G. Jarvis Coffin; c] Hemorrhagic gastritis, Talcott Bates (by invitation). Discussion, Luis Amill (by invitation); d] Xanthomatosis resulting in coronary disease, Wilbur Downs (by invitation). Discus-

sion, John Dietrick (by invitation); e] Acute leukemia presenting a neurological picture at onset, George H. Stueck, Jr. (by invitation). Discussion, Joseph E. Connery; f] Recurrent bilateral pneumothorax with pneumonitis, Charles A. Ragan, Jr. (by invitation). Discussion, Norton S. Brown. ¶ General discussion.

*Section of Genito-Urinary Surgery*—The following were elected at the April meeting of the Section: Chairman, John H. Morrissey; Secretary, Frank C. Hamm; Member of Advisory Committee, John A. Taylor. There was no meeting of the Section in May due to the meeting of the Section of Urology of the Medical Society of the State of New York.

MAY 28—*Section of Obstetrics and Gynecology*. Executive session—a] Reading of the minutes; b] Election of Section Officers and members of Advisory Committee—for Chairman, Frank R. Smith; for Secretary, Harry Aranow; for members of Advisory Committee—(1) Alfred M. Hellman, (2) Edward H. Dennen, for one year (to fill the unexpired term of Francis W. Sovak, deceased). ¶ Presentation of cases. A case of endometrial sarcoma (Specimen—Microphotographs), Henry D. Furniss, C. L. Reid (by invitation). ¶ Papers of the evening—a] Practical consideration of chorioepithelioma, Louis J. Ladin. Discussion, Harvey B. Matthews, David N. Barrows, George Bolling Lee; b] A review of the maternity statistics of New York City for the year 1939, Mr. Thomas J. Duffield, Registrar of Records, New York Board of Health (by invitation).

## AFFILIATED SOCIETIES

MAY 20—*New York Roentgen Society* (in affiliation with *The New York Academy of Medicine*). Presentation of cases. ¶ Papers of the evening—a] The importance of field distribution measurement, Lillian E. Jacobson, M.A. (by invitation). Discussion, Myron M. Schwarzhild, M.A. (by invitation); b] Goldfish as a biological test object in roentgen therapy, F. P. Ellinger (by invitation). Discussion, Giacomo Failla, D.Sc. (by invitation); c] Roentgen therapy in leukemia; survival period and reaction of spleen and nodes, Lucien M. Pascucci (by invitation). Discussion, Ross Golden; d] Roentgen therapy of cancer of the lung; increase in survival period, William V. Tenzel (by invitation). Discussion, Harry Wessler (by invitation); e] Pulmonary and skeletal metastases from cancer of the kidney, prostate and bladder, Jacob R. Freid; f] Treatment of cancer of the ovary, James A. Corseaden (by invitation), Clara Okrainetz (by invitation). ¶ Executive session.

MAY 23—*New York Pathological Society* (in affiliation with *The New York Academy of Medicine*). Case reports—a] A case of extragenital chorioepithelioma in the male, Houston W. Shaw (by invitation); b] A case of massive urolithiasis following massive heparin-sulfapyridine treatment, Arthur Schiffrin. ¶ Papers of the evening—a] Experimental aspects of heparin-sulfapyridine in massive urolithiasis, William Antopol; b] Color photography at the autopsy table, with case illustrations, Jacob Werne, Hans Freivogel (by invitation), Charles Breedis (by invitation). ¶ Executive session.

# BULLETIN OF THE NEW YORK ACADEMY OF MEDICINE



AUGUST 1940

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## FEATURES WHICH SUGGEST PUBLIC HEALTH CONSIDERATION OF RHEUMATIC FEVER\*

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THIS symposium is a part of an effort of the New York Heart Association to focus attention on the public health aspects of rheumatic fever and rheumatic heart disease. About twenty years ago, at the time of the founding of this Association, two points of view were discussed concerning the functions of such an organization: first, educational, to inform the profession and lay public about the importance of the problem of heart diseases with the object of enlisting assistance in setting up institutional care; second, investigative, to study the nature of the problems imposed by various affections of the heart. While the first objective has not been lost sight of, witness the work of the Association of Cardiac Clinics, the second has consumed relatively more thought and energy. Indeed, it is now obvious that the two are mutually coöperative. By establishing a common nomenclature, and developing uniform criteria for diagnosis, hundreds of physicians interested in heart diseases have learned to speak a relatively uniform language. As an edu-

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\* Introduction to the Symposium on Rheumatic Fever, New York Heart Association Heart Committee of the New York Tuberculosis and Health Association Scientific Session at The New York Academy of Medicine, March 26, 1940 (From the Hospital of The Rockefeller Institute for Medical Research)



TABLE I

POSITION OF HEART DISEASE AMONG FIRST THREE CAUSES OF DEATH  
IN NEW YORK CITY AND NEW YORK STATE—1938

Age	Males		Females	
	New York City	Rest of State	New York City	Rest of State
5-14	2nd	X	1st	1st or X
15-19	1st	2nd	2nd	3rd
20-24	2nd	2nd or 3rd	2nd	3rd
25-34	3rd		2nd	3rd
35-39	2nd	2nd	2nd	2nd
40-44	1st	1st	2nd	2nd
45-59	1st	1st	1st or 2nd	1st or 2nd
60-74	1st	1st	1st	1st
75-84	1st	1st	1st	1st
85 and over	1st	1st	1st	1st

X—Not included in list of first three causes.

cational measure, the influence of this book alone<sup>1</sup> has justified that phase of the Heart Association's function, for its wide adoption has made us more conscious of the many kinds of heart diseases with which we have to deal and the necessity for formulating programs peculiar to each kind. Moreover, these commonly used criteria applied to uniform and continuous histories by many cardiologists have made possible a collective type of investigation, supervised by the Research Committee, which now enables us to trace the average life history of various cardiac diseases with a degree of probability much greater than two decades ago. Because so much attention has been paid to rheumatic fever and rheumatic heart disease in so many different places, it now appears that the time is ripe for focusing more attention on the first of the objectives.

Interest in cardiac cripples, particularly children with rheumatic disease, is now being evinced by so many public and private agencies that it is important to take stock of our present position, utilize our accumulated knowledge and project our work so that we may not only institute

TABLE II  
RELATIVE MORTALITY FROM VARIOUS INFECTIOUS DISEASES

	New York City 1938		Philadelphia 1936		New York City 1930-1939
	Number	Rate per 100,000	Number	Rate per 100,000	
Whooping Cough	105	1.40	30	1.5	1206
Epidemic Meningitis	53	0.7	26	1.3	1384
Measles	42	0.56	15	0.7	843
Diphtheria	26	0.35	10	0.5	992
Scarlet Fever	17	0.23	7	0.4	591
Poliomyelitis	4	0.05	2	0.1	693
Total	247	3.29	90	4.5	
Rheumatic Heart Disease	958		357	17.6	
Rheumatic Fever	147				
Total	1105	14.7			
Tuberculosis all forms	3833	50.3	1349	66.4	

good therapeutic procedures, but also continue to gather information by means of which we can criticize both our individual therapeutic and public health programs.

Among the numerous arguments that may be advanced in urging public health consideration of a disease, there may be mentioned: (1) The size of the problem, both absolute and relative to that of other diseases receiving the attention of public health authorities; (2) The nature of the disease; (3) A review of measures which have been applied elsewhere for meeting some of the indications for treatment.

*Size of the Problem.* The absolute number of individuals with rheumatic heart disease cannot be stated, for we lack statistical data based on compulsory notification, except in three small Scandinavian countries. Moreover, in the analyses of vital statistics, the categories covering cardiac diseases are based on anatomical rather than etiologic criteria. Recently, efforts have been made to have the etiologic background entered on death certificates; and analyses of these certificates is yielding useful information. It is also possible to apply knowledge concerning age-linked etiological characteristics to available vital statistics and thus

arrive at some approximate figures. Finally, data collected by various agencies of the New York Heart Association are available. While the problem is world-wide, it seems desirable to limit our discussion chiefly to our local conditions (Table I).

An extract from the first three causes of death in this State and City in 1938<sup>2</sup> shows how relatively large is rheumatic carditis among the death-dealing diseases, for it may be safely assumed that most of the cardiac deaths in the first three decades have rheumatic fever as a background; and also, as indicated later, that in the fourth and fifth decades this infection is an important contributor to the total cardiac fatalities.

More locally, the comparative death-dealing capacity of rheumatic fever and rheumatic heart disease is strikingly brought out by analyses presented in Table II. In the year 1938<sup>3</sup>, in New York City, the six common reportable diseases all together caused less than one-fourth (22%) as many deaths as were reported as due to rheumatic fever and rheumatic heart disease.<sup>4</sup> Nearly the same proportion (25%) was reported by Hedley<sup>5</sup> in Philadelphia in 1936. Only two of these diseases, whooping cough and meningitis, over a period of ten years caused as many deaths as did rheumatic fever and rheumatic heart disease in the single year 1938. Rheumatic fever was reported as responsible for more than one-fourth as many deaths as tuberculosis, in both New York and Philadelphia, and it is highly probable that the reported rheumatic cardiac deaths fell far short of the actual number.

The crippling disease with which rheumatic fever may be compared is poliomyelitis. In the ten year period, 1930-39, there were in New York City, 7811 cases and 693 deaths; but this includes two epidemics, 1931 with 4138 cases and 504 deaths and 1935 with 2054 cases and 91 deaths.<sup>3</sup> This disease properly has elicited wide public interest. Large funds have been raised for care of its victims and investigation of the disease. Because it is reportable, reliable knowledge concerning its incidence can be obtained. The attitude of the laity and public health officials over many years past toward rheumatic heart disease is in striking contrast, even though every year there are more new cases and many more deaths than in the local large epidemics of poliomyelitis.

Moreover, the problems of crippling incident to poliomyelitis and rheumatic fever present quite different features. In poliomyelitis, the maximal damage is inflicted with the first attack; in many instances there is a tendency towards recovery; and one attack confers an immunity to

TABLE III

RELATIVE INCIDENCE OF FATAL HEART DISEASE (RHEUMATIC)  
IN VARIOUS CITIES OF NEW YORK STATE AND NEW JERSEY,  
IN AGE GROUPS 5-24

NEW YORK		NEW JERSEY	
Cities over 100,000	90-95 Rates per 100,000 Age 5-24 1930-1932	Cities over 100,000	90-95 Rates per 100,000 Age 5-24 1930-1932
Buffalo .....	40.3	Paterson .....	29.8
Rochester .....	21.7	Jersey City .....	34.6
Syracuse .....	20.8	Newark (total) .....	22.0
Utica .....	22.2	white .....	21.8
Albany .....	23.1	colored .....	23.5
Yonkers .....	24.3	Elizabeth .....	25.9
New York City (total)	28.0	Trenton .....	22.2
white .....	27.2	Camden .....	18.2
colored .....	45.0		

subsequent infection. In rheumatic fever, on the other hand, one attack seems to increase susceptibility, and while severe cardiac damage may be inflicted early, progressive rheumatic heart disease in children and young adults is generally an indication of continuing rheumatic infection or of repeated attacks. The long-range problem is therefore not alone the treatment of a crippled organ, but the prevention of multiple attacks in people who are peculiarly susceptible to certain infections.

The close parallelism among the various data in New York City and Philadelphia shows that the relative natures of the problems in this area are probably similar. It also seems likely that the incidence of rheumatic heart disease does not differ greatly in the several cities included in the Metropolitan area and in other cities of New York and New Jersey. This is indicated in data abstracted from Hedley's recent analysis<sup>6</sup> of cardiac deaths in the United States among persons between 5 and 24 years of age (Table III). He correctly assumes that most of these deaths are attributable to rheumatic fever. Where the rates have been analyzed

for the two racial groups, white and colored, that for the latter is always higher, at times two to three times that for whites living in the same cities. This is probably an example of the effect of an unfavorable economic environment upon the disease, although it cannot be stated with certainty whether the colored race may have a greater inherited tendency to develop rheumatic fever.

Unfortunately, it is impossible to present figures covering rural populations in New York State and New Jersey. While the disease exists in rural areas, it is evident from an analysis of Hedley's<sup>6</sup> figures in northern tier states that those states with a predominantly rural population have a distinctly lower rate than those with a large or predominantly urban population.

Another way of estimating the mortality resulting from rheumatic carditis is to interpret the deaths reported from heart disease categories 90 to 95, International Causes of Death, by applying to different age groups the etiologic ratios found for corresponding age-groups of cardiac patients during life. The results of such an analysis for New York State for 1938<sup>7</sup> are shown in Table IV.

Such an analysis is obviously open to criticism, which requires consideration. The first objection is the validity of applying the etiologic distribution percentages of Wyckoff and Lingg.<sup>8</sup> They are the best available because they cover not only ambulatory clinic patients, but also those in private practice and in wards. It is of interest that rheumatic fever was an etiologic factor in 42.7 per cent of their total cases, and the same disease was the etiologic background in 40 per cent of the total cases admitted to the New York Heart Association Clinics in the period 1932-39 (see Table V); therefore the total estimated etiologic effect of rheumatic fever on cardiac mortality is probably not far off. The chief question is one of age distribution, for on this rests a very important point in a public health program. Probably the number of rheumatic cardiac deaths estimated in Table IV, in the first four decades, is approximately correct. The number estimated in the next two age-groups appears on first glance too high, but further analysis indicates that approximately this number of older persons probably succumbed to rheumatic heart disease. For example, among 958 deaths recorded as due to rheumatic heart disease in New York City in 1938, only 560 or 58.5 per cent were under 40 years of age; and among the 2114 estimated decedents in the same city and same year, 1230 or 58 per cent

TABLE IV

TOTAL NUMBER OF DEATHS FROM HEART DISEASE—CATEGORIES 90-95  
NEW YORK STATE, IN AGE-GROUP 1-59

Age Years	New York City	New York State (excluding New York City)	See footnote below *	Estimated Number Dead of Rheumatic Fever		
				New York City	New York State	Total
Under 5	16	51				
5-9	72	113	90	65	102	167
10-19	277	424	82	227	348	575
20-29	403	600	75	302	450	752
30-39	751	1138	58	436	660	1096
40-49	2327	3787	29	675	1098	1773
50-59	4539	7714	9	409	694	1103
				2114	3352	5466

\* Per cent figures estimated on distribution of rheumatic fever as etiologic factor of heart disease in various age groups by Wyckoff and Lingg.<sup>8</sup>

TABLE V

RELATIVE POSITION OF RHEUMATIC FEVER AS CAUSATIVE FACTOR  
IN AMBULATORY PATIENTS WITH CARDIAC DISEASE  
IN NEW YORK HEART ASSOCIATION CLINICS

Year	No. of Clinics Reporting	New Admissions		Percent	Total Case Load	If 40 Per Cent of Total Load Due to Rheumatic Heart Disease
		Total	Rheumatics			
1932	51	4318	1915	44.3	14,875	5950
1933	49	3975	1735	43.7	15,314	6125
1934	48	3950	1615	40.8	15,931	6372
1935	50	3911	1588	40.6	16,454	6581
1936	53	3635	1313	36.2	17,487	6994
1937	54	3620	1390	38.2	18,043	7217
1938	56	4064	1506	37.0	19,386	7754
1939	60	3971	1543	39.0	21,209	8483
		31444	12605	40.1		

were in the first four decades. In other words, in both groups about 42 per cent of the total patients dying of rheumatic cardiac disease were over 40 years of age. Hedley<sup>5</sup> records that only 40 per cent of rheumatic cardiac deaths in Philadelphia occurred in persons under 30 years of age, and in similar age distributions of those reported for New York City, for 1938, there were 39.4 per cent in the first three decades of life. All of these parallelisms emphasize the probability that rheumatic fever is numerically a very important causative factor in the cardiac deaths of late middle life, a phenomenon that is often obscured because a far higher proportion of cardiac diseases that occur in this age-period result from the ageing process.

The cardiac disease-inducing potentialities of rheumatic fever may be illustrated in another way.

In the eight-year period, 1932-1939, 12,605 new patients with rheumatic heart disease were admitted to the cardiac clinics of the New York Heart Association, an average of 1575 per year.<sup>4</sup> A breakdown of the figures from which these data are summarized shows that roughly half were children and the rest adults. They comprised 40 per cent of the total cases admitted. If the same proportion of total case-load had rheumatic fever as an etiologic factor, the number of rheumatic cardiac patients treated each year in these clinics would have been between 6000 and 8000. Had this number of cases existed over many previous years, which is highly probable, a total estimation of 2000 rheumatic cardiac deaths per year for the entire city would not seem too high; for we must recall that the figures shown in Table V represent only New York Heart Association clinic patients, and exclude those patients seen in other non-member clinics, private practice and in hospitals. Numerically, therefore, it seems no exaggeration to state that rheumatic fever and rheumatic heart disease comprise one of the major public health problems.

*Nature of the Disease:* While this is not the occasion to discuss extensively the various theories concerning the etiology of rheumatic fever, there are some fairly well-established features that must be considered in their public health aspects. It acts like an infection; and insofar as heart disease is concerned, it is chronic in duration. Moreover, the development of progressive cardiac damage over a number of years in the majority of cases is conditioned by repeated attacks or relapses of the rheumatic infection. This is well-established statistically in children

and adolescents; but it is noteworthy that about three-fourths of patients under forty years of age who succumb to rheumatic heart disease have histopathological evidence of active rheumatic inflammation in their hearts.<sup>9,10</sup> Obviously, scars in the valves, myocardium, pericardium and in the blood vessels must play an important role in heart failure because of the resulting disturbed physiological set-up, but the extent of these anatomical handicaps, in turn, is often conditioned by the number of attacks of rheumatic fever. The importance of affording as much rest as possible to inflamed organs is recognized as a general therapeutic indication; and there are several experiments indicating that normal physiological activity may play a pathogenic role in injured organs,<sup>11,12,13</sup> and degrees of physical trauma, such as slight tapping that would have no appreciable influence on normal tissue, can lead to extensive scarring of slightly inflamed structures.<sup>14</sup> It is interesting that the frequency with which the four heart valves show chronic changes runs parallel to the various degrees of physiological trauma to which they are respectively subjected. While the heart cannot be put completely at rest, measures are clearly indicated that will reduce the work to the minimum so long as there is evidence of active infection. Every reduction of ten beats per minute results in a total saving of about 14,000 beats per day. Therefore, both to favor the overcoming of infection as well as to spare an inflamed organ, facilities for prolonged rest should be extensively provided.

There are some definite factors which appear to favor the onset of rheumatic fever and the appearance of recurrences. Urbanization, with its crowding and great tendency to spread infection, appears to increase the incidence of the disease. Numerous studies indicate the relatively greater frequency with which the poorer classes of society contract rheumatic fever; and the close proximity of these people, one to the other, favors the spread of those types of respiratory infections which are conducive to rheumatic relapses. The relative role of these common environmental features, and of a possible hereditary tendency to develop the disease have not yet been determined in analyses of the well-established family incidence of rheumatic fever. The poorer diets on which the underprivileged subsist doubtless render them less resistant to infections.

This brings up the question of the type of infection that rheumatic fever appears to represent. While no single etiologic agent has been definitely established, it is safe to state that by combining the results of



bacteriological cultures of the upper respiratory tract<sup>15</sup> with those obtained from serological reactions,<sup>16</sup> there is convincing evidence that recent hemolytic streptococcal infections exist in well over 90 per cent of patients with rheumatic fever. These streptococcal infections occur primarily a few days to three or four weeks before the onset of the rheumatic symptoms, and are at times so mild that their presence can only be detected bacteriologically. In epidemics of rheumatic fever among school boys or army and navy recruits,<sup>17</sup> the contagious element seems to be closely connected with the precursory hemolytic streptococcal respiratory infections; and in epidemics of relapses among patients convalescing from rheumatic fever, the spread of the disease from patient to patient can be traced through the spread of streptococci, often of a single serological type.<sup>15</sup> It is quite obvious that only a fraction of patients who suffer hemolytic streptococcal infections develop rheumatic fever; and many patients convalescent from this disease contract hemolytic streptococcal respiratory infections without showing evidence of a recrudescence of their rheumatism; nevertheless, the connection between rheumatic fever and streptococcal infections is so intimate that it can be safely predicted that, could rheumatic subjects be completely protected from this type of bacterial infection, the incidence of relapses and of progressive heart disease would be very materially lessened. As a direct corollary, the building up of resistance against infection and the shielding of these particularly and peculiarly susceptible subjects from this specific respiratory infection becomes an object of public health interest. Whether the problem will eventually be solved by hygienic measures, by immunological techniques, or by chemoprophylaxis is for the future to decide.

On the other hand, there seem to be some definite indications that can be met from our present-day conceptions concerning the nature of this disease during its active stages, and they may be summarized as follows: To build up the patient's resistance against infection; to provide prolonged rest and thus reduce to the lowest possible level the damage to inflamed organs such as the heart and blood vessels; to regulate exercise carefully so that a diseased organ may be slowly restored to its most effective physiological capacity; to provide suitable education in a psychologically proper atmosphere. The chronicity of the disease points to the probability of sanatorial care as being the most satisfactory to meet these indications.

The experience of the London Rheumatism Scheme,<sup>18</sup> which has been slowly developed over a period of fifteen or twenty years indicates that adequate sanatorial and convalescent home treatment for most children with rheumatic fever or active rheumatic heart disease will materially lessen the incidence of permanent heart disease among these patients. For example, in a ten-year period the incidence of acquired heart disease among the school population of London fell from 2 per cent to 0.8 per cent,<sup>19</sup> and there has been a very marked diminution in the number of chronic cardiac invalids among the school children. To make available an average of six months institutional treatment for rheumatic children, London provided between 900 and 1000 beds, a ratio of one bed for each 550 of the school population. Were a comparable number of beds provided for this purpose in New York City, about 1750 beds would be needed. To meet this indication there are now between 300 and 400 beds all supported largely by private philanthropy, but helped by public funds; and the educational facilities are provided by the school authorities. There is no official central agency for the supervision and aftercare of these children, or for the gathering of statistics as to the ultimate fate of patients treated in this ideal way, compared with those who receive the usual home and dispensary care. The Convalescent Care Committee and the Research Committee, in collaboration with many of the Out Patient Cardiac Clinics of the New York Heart Association, are attempting to supervise this work and to learn of the ultimate effects of the various treatments, but at best only a fraction of the total load can be covered by existing committees and machinery.

If we accept as proper treatment an average of six months of institutional care, it is evident that existing facilities are far from adequate; for in a single year, 1934, among about 2100 children with heart disease who were in the wards of the various New York City hospitals, about 85 per cent or 1855 patients remained in the wards less than two months.<sup>20</sup> Indeed, it is both unfair to these hospitals and to the children to ask that these institutions, which are arranged to care for acutely ill patients, should try to provide adequate care for the chronically sick. Economically, the cost per day in sanatoria is less than one-half of that in general hospitals; better care can be provided; and better prophylactic measures can be enforced. The economic effect of preventing progressive heart disease in these patients can hardly be measured.

The provision for institutional care of rheumatic children is only one phase of a large public health problem which this disease imposes, but it seems to be the most promising place to start, because arrest of the infection in its earlier stages would appear to be a sound prophylactic measure in respect to progressive heart disease. It is poor business to care for a child for a certain period and then precipitate him back into an environment where he is liable to suffer a relapse, without attempting to change that environment. Such changing entails educating his family as to the nature of the problem and enlisting their coöperation in instituting better hygienic conditions; it may entail the provision of better housing; it may even demand that the child be moved more or less permanently to a suitable foster home until he reaches a time of life when he is less liable to rheumatic relapses. Many agencies would be involved in a broad gauge program: physicians especially interested in the problem; hospitals and dispensaries; sanatoria and convalescent homes; foster homes; public welfare agencies; housing authorities; school authorities; and departments of health. To coördinate the efforts of all of these agencies would be the function of a properly conceived public health program, which would embrace not only the care of rheumatic children, but of adults with rheumatic heart disease; and combined with it all would be the gathering of adequate statistics over many years, so that eventually it would be possible to evaluate accurately the effect of the whole program and of its component parts.\*

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\* If Departments of Health—City, State and Federal—would publish in their respective Bulletins summaries of the etiologic analyses which are given as secondary or etiologic diagnoses on the death certificates of decedents from heart disease, instead of lumping the primary diagnoses in the categories 90 to 95 of the International List of the Causes of Death, we could even now obtain a much better approximate idea of the death-dealing effects of rheumatic fever. Moreover, the experience gained from making such analyses would be very valuable in framing measures to improve the accuracy of the etiologic data. Because the average duration of rheumatic heart disease is at least fifteen years from the onset of the primary rheumatic attack until the fatal episode, any worthwhile program must be projected on a very long-term basis; hence it is most important to begin collecting vital statistics on as extensive a scale as possible.

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## CLINICAL ASPECTS OF RHEUMATIC FEVER IN ADULTS\*

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THE clinical aspects of any disease may be said to comprise a group of features which in the aggregate tend to identify it as a clinical entity. Some diseases are simple enough in that they have certain pathognomonic features which identify them immediately, while in others the pathological involvement may be so widespread and the clinical manifestations so complex and protean in character as to make it well-nigh impossible ever to be certain of their true character, except by careful sifting and eliminating similar diseases or, more often, by a final anatomic investigation. In the case of rheumatic fever in adults, which is essentially the same as rheumatic heart disease in adults, the clinical picture has such a multiplicity of components and so many elusive features as to render its clinical appraisal one of the major problems in medicine.

Of course, it might be said that every one's own problem is a major one unto himself and that the degree of one's own interest largely determines the magnitude of the problem. However, in the matter of rheumatic fever, those familiar with its natural history will concede at once that, although the juvenile stage of this disease presents numerous perplexing problems, and, while there is a period of quiescence, a sort of a lull, as it were, during adolescence and young adulthood, when carried over to middle age, rheumatic fever leads to problems entirely new and peculiar to this age period alone.

By way of gross comparison, if rheumatic fever, as has been pointed out, manifests itself in childhood as a chronic, protracted illness with recurrent acute episodes of a fulminant nature, it might be added that in the adult its manifestations are largely those of the damage arising out of the inflammations of earlier years. So that, if in the child clinical fea-

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tures of infection seem to dominate the picture, in the adult, especially at middle age, it is essentially or in a large part, the circulatory insufficiency that engages our attention. While in the child, rheumatic fever, by virtue of an overwhelming infection may at times be the direct cause of death; in the adult, it is circulatory failure that generally leads to fatal termination.

It would seem then that in children our primary task would be to check infection and, as far as possible, prevent recurrent episodes in the hope that the resulting damage would be minimal. In the adult on the other hand, we are confronted with the problem of sustaining adequate cardiac compensation and preventing, as far as possible, a complete circulatory breakdown.

From the foregoing gross comparison and from the diagnostic and therapeutic hints which it reveals, it would seem apparent that the adult rheumatic cardiac does indeed present problems of major importance and that, therefore, any discussion of the clinical aspects of rheumatic heart disease in adults should be considered not only for its academic interest but also for its practical aspects. Actually, adequate management of these patients presupposes a reasonable familiarity with at least the cardinal clinical aspects of the disease as it manifests itself in adult life. In this connection, one must be aware also of the fact that in the adult rheumatic cardiac it is not the disease alone that determines the clinical picture. Certain environmental factors, personality equations and accompanying pathological and abnormal physiological states contribute appreciably to its complexity.

The following seem to be the cardinal determining factors in the ultimate clinical picture of rheumatic heart disease in adults: (1) An offending agent, rheumatic fever, which, in one form or another, has persisted in its onslaught for many years. (2) A damaged circulation which, in the course of years, has been leading to an ever decreasing capacity for self expression. (3) An emotional trend which, because of blasted hopes and repeated anxieties, is heading for final frustration. It is the resultant of these that ultimately constitutes the clinical aspects of rheumatic heart disease in adult life.

To portray in some measure of detail the clinical aspects of the disease in adults, it is helpful to consider them in subgroups based roughly on age periods. The third, fourth and fifth decades, for instance, offer a convenient grouping. Young adults below 30 years of age, not unlike

adolescents. tend to follow the juvenile pattern. Their acute rheumatic episodes are probably an expression, at greater intervals, of the recurrent acute features of the disease, as we meet them in childhood. Their cardiac lesions are of the same general type, often multiple; yet, when free from infection, their hemodynamic disturbances in spite of advanced valvular defects are minimal. Their heart action is not particularly disordered and, generally, they are not suffering from any troublesome accompanying diseases.

In the adult of middle age on the other hand, the clinical picture changes entirely and at times quite abruptly. This dramatic change is due, not alone to the infection and not alone to the heart disease as such, but often to certain accompanying conditions which middle age imposes upon the human economy.

In attempting to portray the clinical aspects of rheumatic heart disease in adults, it is convenient to follow the diagnostic patterns of the New York Heart Association as set forth in its Criteria. In doing this, we may inquire successively into (1) the behavior of the etiological factor, rheumatism, (2) the type of anatomic defects, (3) the type of disordered heart action, (4) the degree of functional capacity, and (5) the more common accompanying conditions that make up the complex clinical pattern of adult rheumatic heart disease.

As to the nature of rheumatic fever in adults, it has long been held that the disease is preëminently polyarthritic, in contradistinction to that of children where it is said to be essentially carditic. This distinction is probably more apparent than real. At any rate, it may be challenged on several grounds.

In the first place we must admit that our familiarity with the behavior of rheumatic fever in adults, as compared to our knowledge in the case of children, is limited indeed. Not many years ago we held similar erroneous notions about children. Rheumatic fever meant joint disease, polyarthritis. However, as a result of diligent and extensive study for the past two decades on groups of children under continuous observation from the hospital ward to the convalescent home, to the out-patient clinic, to the school room and into the home, we have learned that, as a matter of fact, the natural history of juvenile rheumatism is entirely different than what we had supposed it to be. We have learned that the disease is actually chronic, often smoldering for months or even years, and that the acute recurrent flares constitute only

a part of the picture. Polyarthritis, we have learned, though at times severe, may at other times be quite mild or not in evidence at all, and yet the disease may be making serious inroads and creating extensive damage.

In adults, not having had the same opportunities for group study, we are seemingly not familiar with the whole disease. This may be due in part to our limited solicitude for adults as compared to children, but mainly perhaps because the adult, having greater responsibilities, will not permit himself to be institutionalized unless he is actually incapacitated by a very painful arthritis or a distressing carditis and therefore is generally not available for uninterrupted observation on a scale that children afford. So on this ground alone, we might hesitate to accept polyarthritis as the representative clinical pattern of adult rheumatic fever.

Furthermore, in adults we are often confronted by another disease characterized by severe polyarthritis, which may easily be confounded with rheumatic fever. I am, referring, of course, to rheumatoid arthritis. The two diseases have so many points of similarity that a differential diagnosis is at times well-nigh impossible and one disease may easily pass for the other.

This is especially true in young adults. The average age at onset of rheumatoid arthritis is between 30 and 35 years. This is an age when acute flares of rheumatic fever are not yet uncommon and when there is still a possibility of an initial rheumatic affection. This is true especially of persons who have migrated from a different climate.

The possibility of a confusion in diagnosis becomes the more apparent if we realize that both rheumatic fever and rheumatoid arthritis may have the same prodromata, the same acute onset with migrating joint pains, and that both have a leukocytosis and an increased sedimentation rate. Competent observers<sup>1</sup> have emphasized that although the differential diagnosis may at times be quite obvious, nevertheless, the two diseases sometimes present syndromata that are surprisingly similar and that they do lead to confusion in differential diagnosis.

There are those, of course, who maintain that we have a reliable means for differential diagnosis in the electrocardiogram. This too, although helpful, is not at all infallible. It cannot offer an ultimate criterion. In fact, at times it may even lead us into a sort of circular reasoning. If the differential diagnosis is doubtful and the electrocardio-



gram happens to be normal, we naturally lean toward the diagnosis of rheumatoid arthritis. After we have accumulated a series of such cases we are apt to generalize and draw the conclusion that the electrocardiogram in rheumatoid arthritis is normal, although our judgment in arriving at the clinical diagnosis of rheumatoid arthritis was initially based upon the fact that the electrocardiogram was found to be normal.

At this point it may be added that the electrocardiogram may not be taken as the sole criterion in any case of heart disease in that it need not be abnormal even in the presence of a carditis. On the other hand, in adults in particular, it may be abnormal without a carditis. Consequently, having no dependable ultimate criteria, a certain number of cases of rheumatoid arthritis of younger adults will be inadvertently included and the clinical tradition that the polyarthritic syndrome represents adult rheumatic fever will be perpetuated.

Adult rheumatic fever undoubtedly has its smoldering stages too. This has been impressed upon us more and more in recent years. Patients who have died from what was believed to be chronic heart failure, without any clinical evidences of rheumatic activity have been proven at autopsy to have active carditis. Still others in whom a rheumatic affection was not even suspected but who were believed to have had, for instance, auricular fibrillation from arteriosclerotic heart disease, have been found at autopsy to have active smoldering rheumatic carditis. The following is a brief description of such a case. It is recorded to illustrate how utterly elusive an active rheumatic carditis may at times prove to be in an adult.

A male patient, 57 years of age, was admitted to the cardiac clinic of the Mount Sinai Hospital (10/17/38) because of fatigue and dyspnea of two years duration. The past history included "typhus" fever in childhood, otitis media at 21 years and a "chronic cough" for approximately 35 years. He was rejected for life insurance at the age of 50 years.

One year prior to admission to the clinic he had a "collapse" accompanied by profound dyspnea. The attending physician's diagnosis was "heart disease and high blood pressure."

Examination on admission revealed a moderately dyspneic middle-aged patient with a rapid irregular heart action and a blood pressure of 210/140. Auscultation failed to disclose any clear-cut evidence of a valvular defect. The following diagnostic pattern was recorded:

- A. Arteriosclerosis, hypertension
- B. Cardiac enlargement
- C. Auricular fibrillation
- D. Circulatory insufficiency

Accompanying condition, transitory glycosuria.

Repeated observation for an entire year revealed no further information. He complained repeatedly of dyspnea, orthopnea and nocturia. Occasionally he was troubled with intermittent claudication. His blood pressure ranged from 170 to 235 systolic and from 90 to 115 diastolic.

On 11/19/39 he had a sudden seizure of severe low substernal and epigastric pain which later involved the umbilical region. Though the pain was agonizing at first, there was some spontaneous relief as a result of which the patient hesitated to apply for hospital admission for two days.

On admission the dramatic picture of mesenteric embolization was evident and prompt operation with extensive intestinal resection was performed. The patient died fourteen hours after operation.

Autopsy revealed a large embolus in the superior mesenteric artery and small thrombi in the left auricle. Examination of the heart revealed, "chronic and acute interstitial mitral valvulitis."

As to anatomic defects and abnormalities in the physiology of the circulation in adult rheumatic cardiacs, it may be said that the younger adults, those below 30 years, present a fair cross-section of the later stages of juvenile rheumatic heart disease. A large number of these have multiple valvular lesions, aortic and mitral which, as we shall see, is not quite true in older age groups. These are survivors, as it were, in a sense that their rheumatic fever has been relatively dormant and that their hemodynamic alterations have not yet produced the wear and tear which in the older age groups definitely contribute to ultimate circulatory breakdown.

The rate and rhythm of the heart in young adults do not differ appreciably from those of children. Rapid heart action is the rule. Irregularities are few. Auricular fibrillation except as a terminal event is uncommon.

The members of this age group, when free from infection, often carry on vigorous physical activities and their circulatory capacity is such that they can successfully combat another bout or two of an acute carditis. Heart failure, except again as a terminal event, is not common among them.

Emotionally they are a mixed group. Some are very hopeful and try diligently to establish themselves. Some strive to acquire training in craftsmanship; others aim at professions. The amount of energy some of these young adult rheumatic cardiacs display in their attempt to gain a foothold is truly amazing. On the other hand, there are those who, either because of a wrong choice of occupation or because having tried and having failed as often, just cannot reach their aim and begin to show signs of frustration. Still others, having consummated marriages under a false pretense, in that they have not disclosed the nature of their

affliction to their mates, labor under a perpetual sense of guilt and live in constant fear of exposure. Emotional factors such as these lead to a disorganization of what otherwise might have been an orderly life. Anxieties soon appear, symptoms begin to multiply, physical findings become colored and the clinical picture turns into a complex jumble, the appraisal of which becomes difficult and will tax the ingenuity of the most seasoned clinician.

Naturally, in many of these young adults, smoldering rheumatic fever is suspected and blood counts, sedimentation tests, x-rays and electrocardiograms begin to adorn profusely the clinical chart. However, a satisfactory appraisal of symptoms and signs is almost impossible until one realizes that in young adult rheumatic cardiacs, strong emotional components enter into the clinical picture of the disease.

Patients between 30 and 40 or, better still, those beyond the age of 40, present an entirely different pattern. Among the anatomic lesions in this group, aortic valvular disease is not so common. Mitral disease (stenosis and insufficiency) is the predominant lesion. This probably means that those with the combined aortic and mitral lesions have by this time largely disappeared from the scene. Furthermore, in this group auricular fibrillation is a common disorder of the cardiac mechanism. At this stage also the altered hemodynamics which have been operative over many years, have wrought havoc with the circulation. Passive congestion of the lungs with its attending breathlessness, embarrassment of the right heart, tricuspid incompetence, enlargement of the liver and peripheral edema begin to appear. Many of these patients are on the brink of heart failure or, in and out of it, as it were. Their functional capacity is low and on the decline. As has been pointed out, many of these older patients undoubtedly harbor active rheumatic fever of a smoldering type. There is reason to believe that, when they lapse into auricular fibrillation, they do so commonly as a result of a subclinical or smoldering rheumatic activity.

The emotional sphere of the middle-aged rheumatic cardiac is also a troublesome one. There is a group, for instance, in whom the menopause has colored the clinical picture. In others we encounter hypertension as a distressing accompanying condition. Both these conditions are characterized by emotional instability and vasomotor imbalance. Besides these, there are any number of other emotional factors that plague the middle-aged rheumatic cardiac.

The all-embracing dilemma of an adult rheumatic cardiac who happens to be the head of a family of minors and who begins to realize that his capacity for work is on the decline, is a familiar one. The influence on clinical symptoms of this type of mental anguish is too apparent to require emphasis.

In order that this presentation may rest on a basis more substantial than mere clinical experience, I had collected from my clinic files, at random, a group of 105 cases of mitral stenosis with or without other valvular lesions. These were examined for initial major rheumatic episodes, clinical evidences of valvular defects and for disorders in heart action. They are listed in the accompanying table.

ONE HUNDRED AND FIVE CASES OF RHEUMATIC VALVULAR DISEASE  
(*Criterion, Presence of Mitral Stenosis*)

Age	Number of Cases	Mitral Stenosis		Mitral Stenosis & Insuffic'y		Mitral Stenosis & Aortic Insuffic'y		Mitral Stenosis & Insuffic'y & Aortic Insuffic'y		Normal sinus rhythm		Auricular Fibrillation	
		No.	Per Cent	No.	Per Cent	No.	Per Cent	No.	Per Cent	No.	Per Cent	No.	Per Cent
13-29	23	0	0	6	26	1	4.4	16	69.6	22	95.6	1	4.4
30-40	41	3	7.3	21	51.3	2	4.8	15	36.6	34	83	7	17
over 40	41	5	12.4	27	65.6	0	0	9	22	32	78	9	22

In approximately one half of these an antecedent major rheumatic episode could not be traced. As will be seen from the table, among those below 30 years of age (23 cases), sixteen or 69 per cent had combined mitral and aortic lesions. Auricular fibrillation was present in only one member of this entire group. In the age group between 30 and 40 years (41 cases), fifteen or only 36 per cent had both aortic and mitral lesions and seven or 17 per cent of the group had auricular fibrillation. In the subgroup beyond 40 years of age (41 cases), only nine or 22 per cent were found to have such multiple lesions and, in this age group, 22 per cent had auricular fibrillation.

This small group is not intended to serve as statistical evidence but merely as an illustrative sample to show that as age advances in adult rheumatic cardiacs, those having combined mitral and aortic lesions are gradually weeded out and that those with mitral lesions (stenosis and insufficiency) have the better chance of survival. It indicates, fur-

thermore, that the tendency to auricular fibrillation rises rapidly beyond 35 years of age.

Prognosis in adult rheumatic cardiac patients is difficult to evaluate. Prognosis is unpredictable at best because the span of life in this group is not determined by the disease alone. Here, too, extraneous factors make their contributions. Although statistical studies indicate an average life span of some 16 years after the discovery of heart disease,<sup>2</sup> such studies fail to tell the whole story unless they specify the social, economic and racial character of the groups under consideration. It is a well-known fact that a sense of insecurity, attendant anxieties and the temperamental make-up of certain groups and individuals, interfere with prophylactic therapy and tend to undermine health out of all proportion to the severity of the disease. Premature death on the one hand and longevity on the other are dependent in an appreciable measure on circumstances not strictly accountable on a cardiovascular basis. Two brief examples will illustrate this point:

Case I: A young woman, 30 years of age, with a mitral stenosis but no traceable antecedent major rheumatic episode claimed to have enjoyed good health, except for about a year, as far back as she could remember. Her mother had rheumatic valvular heart disease (mitral insufficiency) and one of her two children was in the throes of a smoldering rheumatic carditis with a well defined mitral valvular defect. This young woman's temperament could best be described as a cross between that of a highly bred race horse and a wild cat. She was exceedingly sensitive and jumpy, as if to break the barrier at any moment. At other times she would go into the wildest of tantrums. She had reasons, of course. Her husband having absconded, she lived with her invalid mother and had the added responsibility of caring for her sick child. Her income was uncertain in that it depended upon her ability to locate her husband from time to time and to bring him before the domestic relations court where a stipend and a promise would be extracted from him.

This young woman had experienced repeated anxieties and had weathered repeated emotional storms, accompanied by severe pulmonary edema month after month for over a year. In one of these attacks she finally lost her life.

Case II: A sixty-year-old woman with a well-defined mitral stenosis, auricular fibrillation and an advanced hypertension, was seen in an "emergency" because she had a "weak spell" during a dental operation. She gave a clear-cut history of rheumatic fever at the age of 12 years, another at the age of 14 years, and a third episode at about 20 years of age. Each attack lasted 6 to 8 weeks and was followed by an adequate convalescent period.

At the age of 25 years she was married, had two children, both pregnancies and deliveries having been uneventful. Her children were reared with the aid of competent domestic help. Her husband died about 18 years after their marriage and left her well-provided financially.

The patient had no significant complaints up to about 40 years of age when she first experienced "palpitation." Examination revealed "fibrillation." She had

been under competent medical supervision throughout the years and she carried on her limited duties without apparent discomfort.

This patient displayed a remarkable degree of self-composure and an attitude of utter calm. She spoke softly, walked cautiously and never complained, but often volunteered that "life has been good" to her. And so it was indeed, for she had a splendid home, a loyal family, adequate medical attention and a reasonable degree of financial security. She died at the age of 68 years from cerebral hemorrhage. She had lived a quiet, serene and comfortable life in spite of the fact that she had rheumatic valvular heart disease for at least 56 years and auricular fibrillation for at least 28 years.

These cases bear out the contention that heart disease as such, even if advanced and even though it be complicated by well defined hemodynamic disorders, does not necessarily determine prognosis. It is not the status of the heart alone, but rather the status or degree of adjustment of the whole person that determines it ultimately.

The most convincing studies in this connection have been presented by Grant<sup>3</sup> who reported on 1000 cardiac patients under observation for a period of 10 years. These were men of military age, rejected during selection for service, because of heart disease. Having been pensioned and having been placed under competent medical supervision by government agencies, they had a reasonable economic security and continuous medical care. Fully two-thirds of those having rheumatic heart disease, some advanced, were still alive and comfortable at the end of the observation period of 10 years.

#### SUMMARY AND CONCLUSIONS

Rheumatic fever in adults does not seem to conform to a distinctive pattern and the polyarthritic picture suggested by hospital records is more apparent than real. At any rate, it does not represent the whole disease. Smoldering forms are not uncommon and it is this form that probably precipitates insidious failures of the circulation. It is probably responsible also for auricular fibrillation in some cases.

The anatomic lesions in the younger adults are generally multiple but, as age advances, those with combined mitral and aortic lesions are seemingly weeded out. Chances for survival seem best for those who have mitral lesions alone.

Auricular fibrillation, except as a terminal event, is rare in early adulthood. However, as age advances, it soon becomes the dominant arrhythmia and may be present in 20 to 25 per cent of patients past 40 years of age.

Functional capacity in young adults is generally excellent in spite of multiple valvular lesions. At middle age or beyond, it is on the decline and heart failure is an ever present threat.

Accompanying diseases are of minor importance in the younger adult rheumatic cardiac. The greatest hazard is an acute rheumatic episode. At middle age, on the other hand, an accompanying hypertension seems to be the most embarrassing complication.

Emotional factors are present in both groups and color the clinical picture appreciably. Not only symptoms but also physical signs and in a measure even prognosis is influenced by them. They must be taken into serious account in any attempt to appraise the clinical aspects of rheumatic heart disease in adult life.

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## MANAGEMENT OF THE ANEMIAS IN INFANCY AND CHILDHOOD\*

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THE reawakening of interest in hematology following the discovery of the therapeutic use of liver in pernicious anemia was not without its influence in stimulating the investigation of blood diseases in infancy and childhood. It is the purpose of this presentation to discuss the management of the blood diseases peculiar to infancy and childhood in the light of recent advances. Since a predominant characteristic of the blood reactions of childhood is the tendency to revert under stress to embryonic blood formation, this discussion may start from that point.

### FETAL BLOOD FORMATION

Blood formation occurs initially in the wall of the yolk sac and is then assumed by the mesenchymal cells throughout the human embryo. In the sixth week, the liver becomes the site of red cell multiplication and the spleen participates in this function by the end of the second month. In the second and third months, the thymus, mesonephros and the lymph nodes become additional sites of blood formation. While the bone marrow makes its appearance in the sixth week, it becomes actively engaged in hematopoiesis in the third month. During the course of fetal life all of these organs manufacture blood cells with the major activity residing in the spleen and liver. The bone marrow at birth takes over the hematopoietic role of the liver and spleen but in infants and children, when the usual blood sites are strained, compensatory hematopoiesis occurs quite readily in the fetal blood forming organs. The potentiality of blood formation in extramedullary sites persists throughout life, although it is less likely to occur the further the individual is removed from early infancy.

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## THE BONE MARROW IN INFANCY AND CHILDHOOD CLINICAL IMPLICATIONS

So active is the demand for blood cell formation in the infant and young child that all the bones are filled with red marrow. At about seven years of age fat appears, which is grossly observed at puberty. It is only with the appearance of non-functioning yellow marrow that a potential reservoir is created for blood formation when the demand for blood regeneration is increased. In early infancy with the absence of reserve marrow, the need for increased blood formation arising from anemia due to infection or associated with specific blood diseases may necessitate the reactivation of extramedullary fetal sites. Beyond this, when there is need for further room for blood formation, the marrow expands by absorption and atrophy of bony trabeculae and of the cortex. These changes may be sufficiently marked to be visualized roentgenographically as are observed in Cooley's anemia, sickle cell anemia and acholuric jaundice.

The encroachment upon the actively functioning marrow by leukoblastic cells within the inelastic bony skeleton accounts for the bone and joint pain encountered in some instances of leukemia in childhood which makes the clinical differentiation from rheumatic fever so difficult.<sup>1</sup> The roentgenogram, however, often throws light upon the underlying pathological process and discloses generalized or local rarefaction, focal areas of bone absorption and of periosteal elevation. In a study of the roentgenographic changes in childhood leukemia, Baty and Vogt<sup>2</sup> found in 70 per cent of their cases a narrow, transverse zone of rarefaction just proximal to the metaphysis of the long bones, most marked in the lower end of the femora and tibiae. This line may be observed in other conditions, but we have found it a valuable diagnostic aid, particularly when leukemic cells are not yet greatly increased in the peripheral blood.

### HEMATOPOIETIC FACTORS IN TREATMENT OF ANEMIA

In treatment it is important to remember that the erythrocyte-maturing factor found largely in the liver is required for the transition of megaloblast to normoblast. For the final maturation of the erythrocyte iron, copper, vitamin C and thyroxin are probably necessary and for hemoglobin regeneration iron and copper are required. Cobalt

and manganese have also been shown to influence hemoglobin formation but save for iron none of these metals appear in the hemoglobin molecule and probably serve their function as catalysts. In all age groups transfusion constitutes an important element in treatment of anemia by elevating the hemoglobin and red cells, relieving toxemia, reinforcing the supply of hematopoietic principles present in the plasma which control blood formation, and stimulating their normal production. It should be remembered that the completely functioning hematopoietic activities of the adult are not present at birth but develop gradually. To maintain the balance between blood production and blood destruction, maturation and antihemolytic factors are gradually elaborated by the infant and child and until this is accomplished dependence upon fetal stores may be required. It is conceivable, also, that in some infants the development may be slow, and when this is markedly retarded it may account in part at least for such conditions as are included in the syndrome of erythroblastosis fetalis. In accordance with this concept, when prothrombin formation is greatly delayed in the newly born, hemorrhagic disease occurs. It is possible that transfusion stimulates the production of these elements in the infant by acting as an accelerating force in the same manner that it hastens the development of the final blood groups in the young infant. It is possible that frequent transfusions of small quantities of blood may serve the purpose of stimulation more effectively than larger transfusions at longer intervals.

Clinical classifications of anemia are usually based on the predominance of either decreased red cell formation or increased red cell destruction. It will be noted in this presentation that evidences of both deficient blood formation and increased blood destruction may be manifest in the same disorder, although one of these may dominate the clinical picture at a particular time. For that reason there are many anemias which do not yet permit of unequivocal assignment to a definite category such as can now be done with pernicious anemia or with the hypochromic anemia of infants. With Cooley's anemia and in erythroblastosis fetalis, for instance, there have been controversial claims as to classification and until a curative agent is available it will not be possible to settle this problem definitely.

In now taking up the various blood disorders, I should like to point out that in the time allotted it will only be possible to emphasize the

highlights of their diagnosis and treatment since each of these has in recent years become the subject of extensive investigation.

### ERYTHROBLASTOSIS FETALIS

Among the blood dyscrasias of the newborn none has afforded more interest in recent years as regards diagnosis and etiology than the symptom complex of erythroblastosis fetalis. The diseases comprising this group consist of hydrops fetalis, icterus gravis and anemia of the newborn. Although they present a varied clinical picture, they are linked together by certain common features: namely, fetal type of extra-medullary hematopoiesis, abnormal numbers of nucleated red cells in the circulating blood, edema, jaundice, and the fact that successive newborn siblings may be affected by one or the other of these conditions. The gradation of one member of this group into another has been repeatedly demonstrated by cases of icterus gravis with severe edema, and by milder cases of this condition, which during the recovery phase are almost indistinguishable from congenital anemia.

The prognosis of erythroblastosis fetalis is gravest when the signs of the disease are fully established at birth. Cases of hydrops fetalis are usually still-born or die soon after birth, although borderline cases with less extensive edema may survive.<sup>3</sup> When the clinical and hematologic features of icterus gravis are fully established at birth, especially when the jaundice is severe, the outlook is more doubtful than if the disease develops in the course of the first few days of life. With earlier diagnosis and prompter treatment, the mortality from this condition has been drastically reduced.

The most satisfactory treatment of this syndrome consists of transfusion of blood by the intravenous route. The amount of blood with most young infants approximates 20 cc. per kilogram of body weight for each transfusion. It is important to remember that this condition is self-limited and transfusions are supportive in the sense that they tide the infant over the acute stages of the disease until normal blood formation is established. While repeated transfusions are usually required, the intervals between them depend upon the clinical condition of the patient and the state of the blood. Experience has shown that it is unnecessary to attempt to maintain the high hemoglobin and red cell levels which characterize the blood of the normal newborn. Icterus gravis and anemia of the newborn often follow a protracted course and counts

of 2.5 to 3.5 million red cells per cmm. have been found entirely compatible with the well-being of the patients. Unless transfusions are carefully timed, excessive injections of blood may aggravate the hemolytic process instead of checking it. When an infant with a severe form of icterus gravis also presents evidence of toxemia, transfusion should be supplemented by the administration of parenteral fluids.

It has been suggested that an anti-hemolytic substance supplied in utero by the mother controls the hemolysis of red cells in the fetus.<sup>4</sup> With the idea that the infant with erythroblastosis fetalis lacks this principle, injections of serum or plasma from a healthy adult, who presumably possesses this substance, have been advised. Injections of plasma or serum intravenously or intramuscularly, preferably the former, may be useful under certain circumstances. Occasionally an infant at birth possesses normal levels of hemoglobin or red cells but the blood may reveal abnormal numbers of nucleated red cells and the clinical appearance strongly suggests icterus gravis. The introduction of whole blood may still further increase the polycythemic values of the newborn. In such a case the plasma derived from the blood, which would ordinarily have been transfused, may be injected intravenously. The disease at times may show no further progression and recovery occurs. Where possible, it is good practice to give at least one transfusion in addition to the serum injection in order to anticipate any inordinate drop in red cells.

Serum has also been found useful in later stages of icterus gravis and anemia of the newborn at a time when the two conditions simulate each other so closely. Repeated transfusions in the second month of the disease are usually found to be only temporarily effective in elevating the blood levels, whereas repeated intramuscular injections of serum in doses of 10 to 15 cc. are simpler and in some instances have proven of decided value. In the acute stage of the disease, serum or plasma injections are to be regarded as accessory to transfusion and not a substitute for it.

While liver extract has been valueless during the early and acute stages of erythroblastosis, it has been useful during the more chronic stage of the anemia, particularly in those instances when the red cells are still dominantly macrocytic. The liver extract to be employed should not be too highly refined and a cruder one in which each cc. contains no more than two or three units is preferable. The liver is administered intramuscularly in 1 cc. dosage and the number of injections must vary with every case and depends upon the hematologic response.

## HEMORRHAGIC DISEASE OF THE NEWBORN

In addition to the disorders involving red cell maturation and of the forces controlling hemolysis, the factors involved in the clotting of blood may also be affected during the neonatal period and this disturbance is manifested in the clinical condition known as hemorrhagic disease of the newborn.

The tendency to bleed is the result of factors which are operative in the neonatal period. Normally, the coagulation time of the blood is considerably prolonged in the first four or five days of life. Hemorrhagic disease of the newborn must depend, therefore, on impairment in the coagulation mechanism which exaggerates this normal prolongation.<sup>5</sup> Many studies suggest that the clinical manifestations of hemorrhagic disease depend on an abnormal lowering of prothrombin levels which are already reduced physiologically. Bleeding does not occur more frequently because of the rapid conversion of prothrombin to thrombin which compensates for the quantitative deficiency in this substance.

Treatment until recently has consisted almost entirely of blood transfusions. Intramuscular injections of blood have been employed in prophylaxis but their value has been difficult to assess. On the other hand, with the first evidences of bleeding in the newborn the need for blood is urgent and it may be obtained at once from the father or mother and injected without preliminary blood grouping, 10 cc. into each buttock. Any improvement which results must come from the plasma components and products liberated from the disintegration of red cells.

The most effective method of giving blood, however, and the one to be preferred is by the intravenous route, and the dosage is 20 cc. per kilogram of the infant's body weight. The loss of blood may be severe and the anemia may become profound, but the favorable effects of transfusion result not alone from the replacement of red cells, and of hemoglobin, but of prothrombin and of other factors contained in the plasma whose deficiency may contribute to the pathogenesis of the hemorrhage. It tides the infant over until the fundamental disorder corrects itself in the course of development.

With the more recent knowledge that hemorrhagic disease is associated with a deficient prothrombin content of the blood and that vitamin K influences its formation, the most effective plan of treatment consists of combining transfusion with the administration of vitamin K.

Vitamin K is a fat soluble substance whose absence in the diet of chicks was observed by Dam to produce a hemorrhagic disorder. The lowered clotting time of the blood of the chick was soon found to result from a deficiency in prothrombin. Studies following this discovery have eventually resulted in the isolation and synthesis of various substances possessing vitamin K activity. At present the disorders in which vitamin K has been found most useful consist of obstructive jaundice and of hemorrhagic disease of the newborn, both of which are associated with a lowered prothrombin content of the blood.

Several procedures have been followed, directed towards increasing the prothrombin level of the blood of the newly born infant. Vitamin K has been administered to the mother during the last weeks of pregnancy, just before the onset of labor and even during delivery.<sup>6,7,8</sup> This method has resulted in the elevation of both the prothrombin content of the blood in the mother and that of the newborn. Vitamin K has also been directly administered to the normal baby for several days after birth for prevention of bleeding, as well as in treatment of the infant who presents the first evidence of bleeding.

The form and dosage in which vitamin K is to be prescribed have varied a great deal because of the multiplicity of products now available and because of their varied strength. Waddell and Guerry<sup>9</sup> found increased prothrombin levels in newborn infants when they were given a vitamin K concentrate, Klotogen, orally in dosages of 1 cc., 0.5 cc., 0.5 cc., on the first, second and third days, respectively. They found that the same product given to the mother before delivery resulted in an elevation of the prothrombin content of the blood of the infant.

Of the synthetic vitamin K substances, the most active compound to date is 2-methyl-1, 4-naphthoquinone, first reported by Ansbacher and Fernholz.<sup>10</sup> This product has been administered in 1 mg. dosage to mothers before delivery with a resulting increase in the maternal plasma prothrombin as well as that of the infant. It has been given in smaller dosage to the newborn infant, namely, 0.5 mg. for the first 3 days of life, with the same results. This product has also been employed therapeutically in bleeding in the newborn with favorable clinical results. Recent studies have shown that vitamin K preparations may also be administered intramuscularly and intravenously with a resulting increase in the prothrombin content of the blood which is maintained. Whether or not vitamin K administration will be employed as a routine

measure in prophylaxis of this disease awaits the results of extensive trials now in progress.

### NUTRITIONAL ANEMIA

Following the neonatal drop, hemoglobin reaches its lowest level at six weeks to two months of age and remains fairly constant for the remainder of infancy. During the first two years of life the hemoglobin normally ranges from approximately 10 to 12 grams per 100 cc. of blood (equivalent to 70 to 80 per cent).<sup>\*</sup> Nutritional anemia describes the state of the blood in which the hemoglobin values fall consistently below the lower limit.

The period between 8 months and 2½ years constitutes a most critical period for the development of hypochromic anemia.<sup>11</sup> Hypochromic anemia occurs in childhood beyond the period of infancy when growth is again more rapid and the demand for iron is excessive, and this is noted during the period of puberty and especially in girls with the onset of menstruation. In the infant as well as in the older child the problem of treatment involves an inherent difficulty which arises from the lack of data as to the optimum hemoglobin value which will promote maximum growth and development.

The blood of the full-term infant of average birth weight and in good nutrition as seen in private practice usually possesses an average hemoglobin content of 11 gm. (75 per cent) or more after the neonatal period. For practical purposes, therefore, the value of 11 gm. should be designated as the lower limit of normal, although this is an arbitrary figure since it is not unusual to encounter infants, particularly prematures or twins, who are normal in every respect but whose hemoglobin after the second month falls below this value. Particular attention to the hemoglobin level should be directed to all infants who are growing rapidly, to prematures and twins, to those troubled by frequent infections and by gastrointestinal disturbances, and to those whose mothers during the latter part of pregnancy were known to have suffered from severe anemia. With premature infants and twins, it is a good plan to institute hemoglobin estimations during the second month of life and with normal full-term infants these may be postponed until the end of the second or third month.

The choice of iron preparations for the infant as for the adult

<sup>\*</sup> Hemoglobin standard 100 per cent = 14.5 gm. per 100 cc. of blood.

depends upon their acknowledged activity, ease of administration, tolerance, inexpensiveness and solubility. The latter consideration applies particularly to the infant since inorganic salts that are readily ingested by the adult may be unsuitable for the infant. The iron salt should be preferably soluble so that it may be administered in water, milk, or a fruit juice. Reduced iron and saccharated ferrous carbonate possess the disadvantage of requiring a suspension because of their insolubility, but they can be offered to older children. Although there are several soluble iron salts suitable for use in infancy whose efficacy has been amply demonstrated by capable observers, my own experience has been with two of these salts, namely, iron and ammonium citrates and ferrous sulphate. Iron and ammonium citrates may be dispensed in a 10 per cent strength stock solution or in capsules containing the powdered scales. For the infant, the latter are opened before feeding and the contents dissolved in milk, water or sweetened orange juice. It is advisable to offer a small dose of only 5 grains at the outset, since at times vomiting or diarrhea follow its use. In the infant with nutritional anemia of a moderate grade the desired hemoglobin level can be obtained usually with a daily dose approximating 1 grain of iron and ammonium citrates per pound of body weight, which usually amounts to 15 to 30 grains.

Recent studies have shown that iron is more readily absorbed from the intestinal tract in its bivalent form,<sup>12</sup> and that the soluble ferrous salts are most active in synthesizing hemoglobin. Of these, ferrous sulphate has come into popular use, and dosages of 6 to 8 grains daily have been sufficient to produce satisfactory reticulocyte responses and the restoration of normal hemoglobin, red cell and hematocrit levels within a period of from 2 to 3 weeks in infants and young children. It is prescribed in infancy in the form of an elixir, each teaspoonful containing 2 grains of this salt, and the total dose is 3 to 4 teaspoonfuls daily. This dosage of iron we have found on many occasions has served a diagnostic purpose. When 6 to 8 grains of ferrous sulphate daily are administered to an infant or young child with anemia of moderate severity, the absence of a reticulocyte response and a failure of the hemoglobin to return to a level of about 11 gm. per 100 cc. of blood in from 2 to 3 weeks suggest continued severity of an infectious process or that the diagnosis of anemia on a purely nutritional basis is to be questioned. Using this principle, we have been able to uncover several cases of Cooley's anemia in early infancy when no other clinical features had as yet appeared.



With increasing age, the need for iron administration must be gauged in the light of the changing hemoglobin levels of normal children. Hemoglobin levels of 12.5 to 13.5 gm. per 100 cc. of blood are desirable and can be achieved by adequate anti-anemic therapy. The daily dose of ferrous sulphate in older children ranges up to 18 grains, although 9 to 12 grains are usually adequate, and of iron and ammonium citrates up to 90 grains. Because of individual variations in absorption, it must be emphasized here too that the simplest guide to adequate iron intake can only be obtained by repeated hemoglobin examinations.

When maximum doses of iron are required in a child to secure normal hemoglobin levels it may indicate inadequate absorption resulting from diminished or absent free-hydrochloric acid in the stomach. Normal gastric acidity is necessary for optimal absorption of iron from foods and iron preparations in all age periods, and hypoacidity may be a conditioning factor leading to iron deficiency anemias. While this condition has been well known as a factor in the pathogenesis of "idiopathic" hypochromic anemia in older individuals, its existence in children requires emphasis. Many studies have shown that in infants and in children defective gastric secretion is often associated with iron deficiency anemia and that this abnormality persists even when the anemia is cured. It is well known from adult experience that larger doses of iron are required for hemoglobin synthesis in individuals with achlorhydria than in those with normal gastric secretion. Children whose gastric secretion lacks acid should also be watched more closely for recurrence of anemia. There is a gap in our knowledge as to the onset of achlorhydria in those adults who develop idiopathic hypochromic anemia and pernicious anemia. The infants and children with deficient gastric secretion, particularly those who secrete no acid following histamine, may constitute the group of potential cases of these conditions in later life. The administration of hydrochloric acid is without value, however, in facilitating cure of the anemia and produces no response of the marrow as indicated by reticulocytosis.<sup>13</sup>

Increasing evidence points to the desirability of including an adequate quota of vitamins to assure the complete functioning of the manifold hematopoietic phases. In some cases complete recovery has been reported when yeast was employed as a supplement to iron,<sup>14</sup> and recent studies<sup>15,16</sup> indicate that components of the vitamin B complex are involved in hematopoiesis.

Since iron is absorbed in the ferrous form, the reduction of ferric salts to the bivalent form depends upon reducing mechanisms present in the small intestine. It has recently been shown that the administration of cevitic acid with iron salts aids the absorption of iron probably by exerting a reducing action on ferric salts and by preventing the conversion of ferrous salts to the ferric state.<sup>12</sup>

In our experience it has not been necessary to employ copper in the treatment of nutritional anemia, although there are studies to show that its addition in minute traces results in prompt acceleration of hemoglobin production from a previously stationary level.<sup>17</sup> In the occasional infant in whom copper deficiency may occur, as evidenced by a refractory state of the anemia, minute amounts of this element, 1 mgm. daily (equivalent of 4 mg. of copper sulphate) may be included in the iron prescription.

#### COOLEY'S ANEMIA

Fifty years ago, von Jaksch described a condition occurring in infants which he designated as pseudoleukemic anemia whose distinctive features included a severe anemia affecting red cells and hemoglobin, extreme degrees of leukocytosis, occasional enlargement of the lymph nodes, slight increase in size of the liver and a marked splenomegaly. He differentiated this disorder from the anemia of rickets which showed a lesser degree of leukocytosis and particularly from leukemia with which it might most often be confused. He pointed out that the outcome in the disease he described may be favorable. Although von Jaksch separated pseudoleukemic anemia from the anemia of rickets and emphasized the features of marked leukocytosis in the former, many poorly defined anemias of infancy and childhood were gradually placed in the category of von Jaksch's anemia which were very often associated with infections, rickets, syphilis, and nutritional deficiencies.

In 1925 and in 1927, Cooley and his associates drew attention to an anemia which had heretofore been regarded as belonging to the heterogeneous group of von Jaksch's anemia, but which possessed such well-defined features as to constitute a definite clinical entity. Outstanding characteristics are its racial and familial tendencies, the skeletal changes, and the appearance of large numbers of circulating normoblasts.

With few exceptions, an important diagnostic feature of this condition has been its racial limitation to children one or both of whose

parents were born in northern Mediterranean countries, especially Italy, Greece, or Syria, and most frequently in Sicily. The disease begins insidiously early in infancy and is usually sufficiently advanced in the second year so that it can be recognized clinically. In severe cases the disease is fully developed early in life and its course is relatively short. Milder cases pass unrecognized until later childhood. There is evidence that, like hemolytic jaundice, it can occur in healthy members of the family in latent form so that inheritance is a possibility. It is also possible that there are individuals with mild forms of this disease who may perhaps be suffering with an unexplained low grade chronic anemia. This disease has been referred to as the erythroblastic anemia of Cooley, or from its racial limitation the term, Mediterranean anemia or thalassemia was suggested by Whipple and Bradford.<sup>18</sup>

In its fully developed form the symptoms are pallor, weakness, headache, bone pains, bouts of fever, anorexia and vomiting. The abdomen protrudes when splenomegaly becomes pronounced; the liver is enlarged to a lesser degree and lymphadenopathy is slight. Other important features include frontal and parietal bosses, prominent malar eminences, depression of the bridge of the nose, from which epicanthal folds arise lending an oblique appearance to the eyes, enlargement of the superior maxilla so that the lip is pushed upward often exposing the upper teeth, a muddy yellow complexion, prominent eyes whose sclerae may show a tint of icterus which is intensified at times. These characteristics combine to lend a mongoloid appearance to the patient and account for well-known resemblance of the affected children to each other rather than to their normal sisters and brothers.

The blood shows a moderate to severe anemia, leukocytosis, often with early myeloid cells, a reticulocytosis, an elevated icteric index, numerous nucleated red cells which are remarkably increased after splenectomy and a striking resistance of the red cells to hypotonic saline in fragility tests so that in some instances the red cells are not entirely hemolyzed even in distilled water.

In established cases of Cooley's anemia, in addition to erythroblastosis the red cells manifest polychromatophilia, poikilocytosis and anisocytosis. While variously shaped microcytes are present, the most important for diagnostic purposes are macrocytic cells containing little hemoglobin which appear in great numbers and whose size is sometimes of unusual proportion. At least three types of macrocytic red cells

characterize the blood in the various clinical types of Cooley's anemia but all types possess the fundamental characteristics of the red cells in this disease; namely, abnormal thinness. One of these is a non-specific type designated as a target cell, named so by Barrett<sup>19</sup> because of its deeply stained center and periphery which are arranged in concentric light and dark zones. The second type of macrocyte is usually a round or sometimes slightly oval cell with a narrow rim of hemoglobin of varying thickness with a large zone of central achromia in which a faintly stained island of hemoglobin may occasionally be discerned. The third or most specific type is a large, pale erythrocyte described by Cooley which contains irregularly distributed hemoglobin which is clumped and whose intervening areas seem to possess staining defects. This cell is extremely thin and leaflike and in wet preparations its edges are observed to fold over and the several layers thus formed possess a remarkable transparency.

X-rays of the skeletal system reveal the evidence of extreme hyperplasia of the bone marrow by osteoporosis, thinning of the cortex, trabecular atrophy, coarse reticulation with the regeneration of new bone, which is a later development in the disease, and thickening of the skull. Caffey<sup>20</sup> found that the frontal bone was the site of early and marked thickening and in one of our cases this served as a clue to the diagnosis in the first year of life. In severe cases, increased porosity may also be noted in bones of the pelvis, vertebrae, ribs, clavicles and scapulae. Lateral views of the skull show an enlarged diploic space which is either finely granular or mottled, or striated. The vertical striations give the appearance of "hair standing on end," which seem to extend beyond the outer table. The earliest signs are observed in the small bones, particularly in the metacarpals and metatarsals and reveal osteoporosis and expansion of the medullary cavities, producing a rectangular instead of the normal concave appearance. The greatest opportunity for skeletal changes is in the soft and elastic bones of the infant and least in older children. Cortical thinning may be so extreme as to result in pathologic fractures.

There is no specific treatment for Cooley's anemia, and iron, copper, liver, and extracts from spleen, pancreas, adrenal, and other endocrine products, high calcium diets, large dosages of vitamin B and D, plasma and cell extracts, x-ray therapy have all been used without effect. At the suggestion of observers that this disease may in some instances repre-

sent a congenital form of malaria, we have given quinine in large dosage and have found no alteration in the blood picture. On the other hand, Caminopetros<sup>21</sup> observed reduction in the number of nucleated red cells and of white cells following malarial therapy.

The only measures which are of value in modifying the course of the disease are transfusions and splenectomy. Splenectomy has usually been recommended to relieve the child from the weight and pressure effects of a greatly enlarged organ. With the earlier recognition of this disease, as is sometimes possible with the aid of the roentgenogram, careful blood studies, and its suspected recurrence in an affected family, the problem that is presented concerns the desirability of removing the spleen before it becomes too large, before the liver undergoes enlargement and before extensive skeletal changes set in. The results in early cases thus far show that while splenectomy affords no cure, it prolongs life; but the choice of cases and optimal period for this operation await further study. In the case reported by Stillman and Hitzrot the patient lived for 18 years following the operation.<sup>22</sup>

Since the disease is only in part hemolytic and is probably fundamentally due to a deficiency of unknown hematopoietic principles or to a metabolic disturbance, splenectomy can only be expected to modify the disease slightly. However, when the hemolytic activity is extreme, splenectomy is most essential.

One of the prime indications for splenectomy has been in the reduction of the number of transfusions that are sometimes required to maintain life. In some of our cases where frequent transfusions were needed, splenectomy has succeeded in lengthening the interval between them. The elevated levels obtained by transfusions are only temporary and the blood soon drops to a point below normal at which a hematopoietic equilibrium is established and at which daily activities can be carried out without restriction. We have several children under observation who appear to be comfortable and require no transfusion for indefinite periods with hemoglobin values from 8 to 9 grams per 100 cc. of blood (50 to 60 per cent), and red counts usually between 3 to 3.5 million cells and in a few instances of from 2.5 to 3 million cells.

#### VON JAKSCH'S ANEMIA

The question remains whether there is any further need for the term von Jaksch's anemia, particularly since the definition of Cooley's

anemia as a disease entity has removed so many cases from the earlier designation. In addition, advances in hematology have eliminated other cases which were truly secondary anemias, so that in this country at least the diagnosis of von Jaksch's anemia is at present made infrequently. In the light of modern hematological studies the greatly increased leukocyte counts with anemia noted by von Jaksch may have been leukemoid responses to infection, as well as responses in severe hemolytic anemias, deficiency anemias accompanied by infection and possibly to syphilis, especially in young infants.

English pediatricians, however, apply this term to a secondary subchronic hemolytic anemia resulting from infection, gastrointestinal and nutritional disturbances occurring in children under 3 years of age. It seems to me that this term should be reserved for a condition possessing the features originally described by von Jaksch and his contemporaries; namely, a blood disorder of infants and children which shows a reduction in hemoglobin and red cells, a pronounced leukocytosis, nucleated red cells, a greatly enlarged spleen and a smaller liver, and whose outcome is often favorable. A case should be excluded from this classification when it is now possible to assign it to a more definite category or when the etiological factor is known.

#### LYMPHOCYTIC BLOOD PICTURES

Exaggerated lymphocytic reactions are especially difficult to interpret in infants and young children because a predominance of lymphocytes and a greater lability of the blood forming mechanism constitute normal features of the blood of this period. Not alone is the cause for a lymphocytosis often puzzling, but the structure and staining reaction of the cells may differ in important details from the adult patterns and, therefore, arouse suspicion of a possible blood dyscrasia. It is at this age period in particular that the differentiation between infectious mononucleosis, lymphatic leukemia and a lymphocytic response to infection is often difficult.

During the first week of life the number of polymorphonuclear leukocytes exceeds that of the lymphocytes; by the end of the first week they equalize each other, after which the lymphocytes predominate for the remainder of infancy. From the third to the fifth year these cells again approximate each other numerically and following this the granulocytes slowly increase to the adult values of about 60 per cent and lympho-

cytes decrease to from 25 to 30 per cent, levels which are usually achieved at about 12 years. Lymphocytic percentages usually do not normally exceed 60 per cent from six months to two years, 50 per cent to the end of the sixth year, 45 per cent by the eighth year and 40 per cent thereafter to adult periods. It is important to emphasize that for the true assessment of lymphocytosis absolute values must be considered. Lymphocytes may be present in normal numbers but their increased percentage when the granulocytes are suppressed and when the total count is reduced may lead to a false impression. To avoid misinterpretation, certain figures will prove of value; namely, that the maximal normal values for lymphocytes grade down from 7000 at one year to 6000 at four years and then slowly to 4000 at puberty. These are, of course, only approximate values and variations may be due to physiologic fluctuations, to differences of technique and to the chance distribution of cells.

#### I. INFECTIOUS MONONUCLEOSIS

Infectious mononucleosis in children, as in adults, is an acute infectious disease occurring epidemically or sporadically and characterized by a prodromal period of malaise, anorexia, listlessness, followed by fever, pain in back of the neck, enlargement of lymph nodes, sore throat, palpable spleen, a characteristic blood picture chiefly affecting the lymphocytes. It offers an excellent prognosis. The clinical manifestations are extremely variable, and this applies to such an important diagnostic feature as lymphadenopathy.

The characteristic blood changes involve the white cells, whereas the hemoglobin and red cells remain normal during the acute stages of the disease. At about the second week of the disease with active glandular enlargement the white count ranges from 12,000 to 15,000, with values frequently below and above these extremes, and of these, the mononuclear cells average as high as 40 per cent to 80 per cent. Their classification is attended with difficulty but supravital studies have established their identity as lymphocytes although monocytes may also be somewhat increased. The blood smear shows a shift to the left of granulocytes and considerable numbers of normal small, medium and large lymphocytes. The characteristic cells are atypical and possess morphological characteristics which distinguish them from normal lymphocytes. They are larger than normal; their cellular edges are often

ragged and irregular; the cytoplasm is usually abundant and stains darker blue with the Wright stain than the normal large lymphocyte. The shade varies from a slate-color to the deep basophilia of a plasma cell and the latter is often limited to the margins of the cell. The cytoplasm contains fine or coarse azure granules and one of the most striking features is vacuolization of the cytoplasm.

The nucleus may be round, oval, kidney-shaped, occasionally divided and often eccentrically placed. The chromatin consists either of deeply staining clumped masses, as in the normal lymphocyte, or it may possess a more immature pattern in that the chromatin is composed of finer strands demarcated from the parachromatin and staining more lightly. The fenestration or holes in the nuclei of the lymphocytes which were described by Osgood<sup>23</sup> as peculiar to this disease are also occasionally observed.

The discovery by Paul and Bunnell that the blood serum of patients with this disease is able to clump sheep red cells in dilution considerably above the normal titer introduced an important diagnostic measure. The heterophile antibody test is practically specific, and by appropriate absorption tests it is possible to exclude the elevated titers sometimes encountered in normal persons and in those with serum sickness. While a positive serology is present in most instances, children, perhaps more than adults, frequently show a typical blood picture with a negative serology.

## II. LEUKEMIA

Leukemia in childhood may for a considerable period of its course be unassociated with an enlarged spleen, lymph nodes or a leukocytosis, so that the true nature of the disease is unsuspected. The blood smear at this stage may reveal an unexplained lymphocytosis but close examination reveals that some of the lymphocytes are morphologically abnormal.<sup>1</sup> In this condition the immature cell varies in size from that of a small lymphocyte to one twice or a little more in size. These cells are lymphoblasts and differ from the cells of infectious mononucleosis in many respects. Lymphoblasts are usually round, more uniform in size; the cytoplasm—though basophilic—is scantier, and when vacuoles are present they are fewer and two to three times the size of those in infectious mononucleosis. The essential diagnostic feature rests, however, in the nucleus where, instead of masses of dense basichromatin as



found in the normal lymphocyte, the chromatin stains lightly, is finely granular, stippled or sieve-like, and shows the presence of nucleoli. The nuclei of the immature cells found in infectious mononucleosis on the other hand possess a greater condensation of chromatin.

### III. CHRONIC NON-SPECIFIC INFECTIOUS LYMPHOCYTOSIS

Perhaps of greater importance clinically than either infectious mononucleosis or leukemia is the occurrence of a lymphocytosis in childhood which is especially common in the early years of life and which cannot be assigned to either of these categories or to other causes producing a similar blood reaction, such as influenza or typhoid fever. It is undoubtedly associated with a low grade infection, often of the upper respiratory passages and sinuses, and for weeks and months anorexia, listlessness, irritability, easy fatigability, and occasionally paraumbilical pain are common complaints. Physical examination reveals a slight reddening of the fauces, occasionally a postnasal discharge; infrequently palpable superficial lymph nodes of small size, especially in the cervical region, and the edge of the spleen may or may not be felt.

Examination of the blood shows a mild anemia affecting the hemoglobin more than the red cells; a white count from 6,000 to 15,000 of which the lymphocytes average from 50 per cent to 80 per cent; and the *Paul-Bunnell* test is *negative*. Examination of the lymphocytes reveals that they are in the main of the small and intermediate variety, that the nucleus consists of heavy chromatin masses like the normal lymphocyte but that the cytoplasm is scanty and basophilic. As is common in the blood smear of all children, an occasional cell is of the large variety and possesses a moderate basophilia and a nucleus slightly lighter staining than the normal large lymphocyte. In effect, the entire appearance of the cells represents a shift to the left of lymphocytes comparable to that of polymorphonuclear cells during infection. I believe the term which best describes this condition is chronic non-specific infectious lymphocytosis.

These cases give no antecedent history resembling infectious mononucleosis even though a few cells resemble the abnormal lymphocytes of that condition. There is no ground for regarding blood responses of this type which are usually based on infection as cases of infectious mononucleosis. The latter term should be restricted to a definite clinical syndrome, even though its etiology is as yet unknown. Non-specific

infectious lymphocytosis runs a prolonged course during which the child is susceptible to acute infections of the ear and throat. Besides treatment of the upper respiratory infection, therapy should include large doses of iron and other anti-anemic agents which serve not alone to elevate the hemoglobin but have also been observed to expedite the restoration of a normal white cell picture.

#### BONE MARROW EXAMINATION BY STERNAL PUNCTURE

The value of bone marrow examination in the study of blood dyscrasias has long been recognized, but because biopsy involved a surgical procedure its employment has been limited. With the demonstration that the sternum was superior to the tibia as a source of active bone marrow and that an adequate specimen could be obtained by needle aspiration, bone marrow studies are now commonly carried out when the blood smear is found to be inadequate in diagnosis.

In infants and children bone marrow studies have been extremely valuable because the peripheral blood does not always completely mirror the extent of the disturbance. While normal data for the cellular content of bone marrow in early ages are still limited, certain qualitative and gross quantitative alterations can be readily ascertained.

It has already been stated that leukemia in childhood may for a period reveal no typical changes but bone pains, but an anemia more severe than can be accounted for by rheumatic fever leads to the suspicion of a blood dyscrasia. At a time when the white cells show very few if any changes in the peripheral blood, the bone marrow may be completely replaced by the blast cells of leukemia.

In diseases of abnormal lipoid metabolism, the sternal smear reveals the diagnostic Gaucher's cells characterized by striated or fibrillar network in the cytoplasm, or the typical foam cells of Niemann-Pick's disease. Sternal aspiration may assist in clarifying the early diagnosis of hemolytic jaundice and of Cooley's anemia by the pronounced cellularity of the bone marrow with normoblasts over 50 per cent of all cells. On the other hand, in a condition in infancy and childhood known as hypoplastic or chronic congenital aregenerative anemia, marked from birth by an anemia requiring frequent transfusion but with no effect on any other blood elements, the bone marrow shows very few nucleated red cells.

When sulfanilamide or sulfapyridine is administered over prolonged

periods, granulopoietic depression may occur with extremely low leukocyte counts. Quantitative measurements reveal a diminished cell content with a differential picture which varies from an almost complete suppression of all granulocytic elements to a maturation arrest at one of the earlier developmental levels. Further treatment should be controlled by marrow studies which include a qualitative and quantitative survey of both red and white cells.

Acute purpura occurs more commonly in infants and children and the chronic form more in adults. In children it is often ushered in by an infection, and spontaneous recovery is frequent without repetition of the episode. However, chronic cases usually and eventually require splenectomy. In purpura a hyperplasia of megakaryocytes is observed in the bone marrow, but separation of platelets from their cytoplasm is not observed. Splenectomy probably removes an inhibiting factor and following operation the megakaryocytes are reduced to more normal levels. It has been stated<sup>24</sup> that a diminution in the megakaryocytes serves as a contraindication to splenectomy and, if corroborated by further data, this will constitute an important guide to the selection of cases for operation.

### CONCLUSION

Recent contributions in hematology have thrown a great deal of light upon the interplay of forces which maintain blood equilibrium. The diverse blood pictures outlined in this presentation indicate that certain essential hematopoietic factors are still unknown and await discovery. The detection of blood disturbances and discernment of the finer diagnostic morphologic details of reacting blood cells lie within the province of every practitioner by the painstaking use of simple instruments and techniques. In infancy and childhood the observations must, however, be interpreted with reference to the changing blood levels accompanying normal growth. With the guiding principle that anemia represents a symptom rather than a disease, and by a diligent search for a deficiency or other causative factor, rational treatment can then be instituted by the judicious administration of the few but reliable anti-anemic agents.

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## CONVALESCENCE IN CORONARY DISEASE

With Special Reference to THE SARATOGA SPA THERAPY

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IT WOULD appear timely both because of the season and especially because of the lack of availability of the foreign spas again to put before the medical profession the similar advantages which the State of New York has provided at Saratoga Springs. There is wanting none of the essentials and in many respects there are features of superior advantage. The extensive physical equipment is in wooded terrain on a state reservation of something more than a thousand acres. The bath houses, drink hall, recreation center, hotel, laboratories, paths have been built upon a long-considered and well-conceived plan. Much has been done to beautify the scene and to provide simple and suitable amusement.

The advantage offered is greater to the chronically ill and to the convalescent. Of the chronically ill, those suffering with some form of heart disease and especially degenerative heart disease seem to receive much benefit. The treatment emphasizes more hygiene of life than drugs. It endeavors to teach a suitable way of living for the individual and has to do largely with rest, relaxation, exercise, diet and the teaching of a calm, philosophical outlook in general and upon the cardiovascular handicap in particular. Also it has to do with the matter of a mineral bath, the essence of which is CO<sub>2</sub> gas, an agent of considerable potency as a cardiac and respiratory stimulant and as a vasodilator.

In 1936 a survey was made of patients coming to Saratoga for treatment. Only those under the physician's care were counted, in order to achieve more than an impression of the number and type. This study showed 4,352 patients to have been under supervised care and, of this number, 1,425 or 32.7 per cent suffered from some affection of the cardiovascular system. Of these 1,425 patients more than 60 per cent were in the category of coronary disease. The patients are ambulatory to a greater or lesser degree and the regime is adjusted to the individual capacity. These patients usually come from the modest or the well-to-do categories, but it is of interest that a yearly average approximating

20 per cent are on a non-paying basis, and are largely from the dependent group.

The general plan of treatment entails a fairly thorough organization of the patient's day. The matter of rest periods is one of the first things to be discussed. The bath hour is sufficiently late in the morning so that no sense of hurry is engendered. There is a rest period of an hour following the bath, and another one after lunch. Often the patient is advised to lie down a half hour before dinner and some patients spend one period of 24 hours a week in bed. All patients retire by ten o'clock, theoretically at least, and for the most part they do.

A word about the management of the baths should be of interest. These are given variously: every other day, two baths successively followed by a rest day, or three baths successively followed by a rest day. A careful estimate of cardiac status determines the number of baths given successively as well as the amount of skin exposed to the gas, i.e., the height of the water as the patient sits in the tub; the percentage of gas in the water and the duration of the bath. The reaction to the bath, favorable or otherwise, dictates changes in these variables. A favorable reaction would be a slowing of the heart rate, a sense of relaxation, hyperemia of the skin and increased urinary output. In the hypertensive, a fall in pressure synchronously with a slowing of the heart rate would be an auspicious reaction.

Cardiologists in general are agreed that hearts are bettered for taking some part of the amount of exercise which they can tolerate without embarrassment. Since our patients are all ambulatory, the determination of how much and of what type is an important one. This exercise period comes in the afternoon, following the post-midday meal rest-hour. It consists of walking at a stated pace for given time periods on the level paths about the reservation. The walk has been made attractive since these paths are largely in wooded terrain, and among pine trees. Rest benches are placed at frequent intervals.

Occasionally, it seems desirable to sugarcoat the pill of exercise, and for this purpose a golf course has been designed. There is no gradient on it over four degrees, and no long holes. The amount of work done may be graduated simply by utilizing clock golf in the beginning, and progressing from a pitch-and-putt game to a full nine holes. For patients of materially lessened capacity, massage and passive and active exercise are used.

The conquest of fear is not one of the least important things to be undertaken. During the course of his stay there are occasions for many talks with the individual, since he is seen almost daily. An attempt is made to create an optimistic adjustment to the individual handicap, and to stimulate interest in things within this handicap. It is stressed that there is no need to give up everything in life, only to learn to stay within the safe limits of capacity. Parenthetically, this is not always so simple to determine. It varies too much from day to day. So, by frequent and careful observation it is sought to evaluate and to advise suitable work and diversion and to stress the positive rather than negative factors. There are two particular phobias which give much concern: fear of blood pressure, and fear of meat. It would seem that in too many instances these have been permitted to cause too much restriction in living.

It is desirable to eliminate the unnecessary burden of obesity insofar as the reduction is consonant with the safety of the individual. The stay at a convalescent center creates an excellent opportunity to effect indicated reduction. In the experience here most patients can lose safely two to three pounds a week, which in our experience necessitates diets of less than a thousand calories. More calories than this effect no weight loss on the regime as outlined.

It may be well to say a little about the teaching of the conduct of life in the coronary case, for at a convalescent center, as at the sanatorium for the tuberculous, a rare opportunity is given to help the patient to make his adjustments. Education concerning the "red flags" is particularly indicated, and of these, that of a sense of exhaustion should be emphasized. Precordial distress and shortness of breath are less frequently passed over lightly by the patient. A sense of exhaustion is so often seen in this type of heart disease, especially in patients showing bundle branch or arborization block, and this appears before evidence of early congestive failure. It calls for restriction of activity.

We teach emotional stability, particularly with regard to the minor irritations of life. A sense of humor, a calm and somewhat fatalistic philosophy, and a slower tempo of life are stressed. We emphasize too, keeping as physically fit as capacity permits.

No time is spent in the discussion of the value of the carbon dioxide bath. It is a matter better to be proven or to be disproven by future research. It cannot be separated easily from the whole regime employed,

and so is difficult to evaluate. Certainly, it is psychologically important and in no sense would one wish to say that it is of no value from the standpoint of actual therapy. Well-considered opinion indicates on the contrary that it has value.

Briefly then, this paints with a few broad strokes the picture of the treatment of the cardiovascular patient at Saratoga Springs. The principles employed are simple but of basic importance. In a goodly percentage of cases they have been helpful.



## ANNOUNCEMENT OF A STUDY TO EVALUATE ORIGINAL SEROLOGIC TESTS FOR SYPHILIS

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More than five years ago the Committee on Evaluation of Sero-diagnostic Tests for Syphilis, in coöperation with the United States Public Health Service, conducted a study to evaluate original serologic tests for syphilis or modifications thereof in the United States. The results of this study were published shortly after the investigation was completed.<sup>1</sup>

Consideration is now being given by the Committee to the organization of a second evaluation study of original serologic tests for syphilis or modifications thereof within the next year. If the need for an investigation of this kind seems to justify the cost, invitations will be extended to the authors of such serologic tests who reside in the United States, or who may be able to participate by the designation of a serologist who will represent them in this country. The second evaluation study will be conducted utilizing methods comparable to those employed in the first study.<sup>2</sup>

Serologists who have an original serologic test for syphilis or an original modification thereof and who desire to participate in the second evaluation study should submit their applications not later than October 1, 1940. The applications must be accompanied by a complete description of the technique of the author's serologic test or modification. All correspondence should be directed to the Surgeon General, United States Public Health Service, Washington, D. C.

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<sup>1</sup> *Vcn. Dis. Inform.*, 1935, 16: 189; *J.A.M.A.*, 1935, 104: 2083.

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# BULLETIN OF THE NEW YORK ACADEMY OF MEDICINE



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## THE PROBLEM OF AGING

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It is remarkable that the problem of aging, one which has existed since the beginning of the human race, should have excited so little interest and been so largely neglected until recent times. Long before Cicero delivered his often quoted oration on Old Age, scholars exhibited a philosophical interest in the process of aging. Later, the pathological aspects of the subject excited some attention but the subject of old age as a far-reaching, vital problem of great medical, social and economic importance, has only aroused active discussion within the past decade.

The problem was of little general interest because until recently it could hardly be said to exist. A consideration of the changing trends in the age of the population, particularly of the western world, throws light on this question. This aspect of the problem of aging has been well discussed in the suggestive contribution of Louis I. Dublin in the admirable group of essays sponsored by the Josiah Macy Foundation in which are presented in a scholarly way, the biological and medical aspects of the aging process.

This subject involves a discussion of life span and life expectancy. The restricted and proper definition of life span is the limit of duration beyond which individual human life does not extend. It is almost impos-

sible to find accurate data based upon authentic records upon which to compute life span. Most authorities are in agreement that, in all probability, life span has varied little for many generations and that the one-hundred-year length of life is rarely exceeded by man.

In contradistinction to life span is life expectancy, which is computed from life tables from which may be reckoned the expectation of life at any age. As Dublin well puts it: "The life table shows what would be the number of survivors to successive ages, what would be the number of deaths at successive ages and what the expectation of life would be if the death rates at each age remained constant as of the calendar year or period for which it is constructed."

From a study of the life tables constructed for various periods, striking results may be obtained. It has been estimated that the mean length of life in the days of the Roman Republic was between 20 and 30 years. This life expectancy at the end of the 17th century had only advanced to 33.5 years. In a country such as Sweden between 1755 and 1776 the mean length of life was only 34.5 years. Life tables constructed for that country between 1816 and 1840 showed that life expectancy had only increased 7 years. From 1861 on, tables were constructed for successive 10-year periods. These showed a steady upward progress in life expectancy; from 44.6 years to 57 years for the period between 1911 and 1920 and during the next decade, the expectation of life had reached 62.3 years. In the early days of this Republic, a little more than a decade after the Declaration of Independence was signed, the mean length of life has been estimated to have been 35.5 years. From Massachusetts life tables in 1850, life expectancy had advanced to only 40 years. From the beginning of the 20th century on to the present, longevity in the United States has steadily advanced. In 1900 it was about 50 years. Twenty years later it had reached 55. The tables for 1930 show that it had passed 60 years and an analysis of the past decade unquestionably indicates a still further increase in the expectation of life.

There are certain basic factors which are largely responsible for the marked improvement in longevity that has taken place during the last half-century. A study of the figures makes it clear that this gain in life expectancy has been largely centered in the earlier years of life. In white males the expectation of life at birth in 1901 was 48.23 years; by 1931 this had been increased by 10.61 years. On the other hand, during the productive period of life which reaches its height at 40, the increase in

longevity was only 0.74 years and during the latter years of life, the gain that occurred was negligible. The situation with white females was essentially the same although the gains that occurred were slightly greater. It is reasonable, therefore, to conclude that this prolongation of life which is limited practically to the younger age groups, has been due to the control of those conditions that are known to be particularly destructive of youth. It is significant that this upturn in longevity took place coincidentally with advances in the control of the various infectious diseases, with the lessening of infant mortality and the awakening of the national conscience in matters pertaining to public health, sanitation and general improvement in living conditions. Coincidentally with the increase in life expectancy, has occurred a marked drop in the mortality rate over this same period, notably in the first 10 years of life, whereas the mortality rate in the higher age brackets varied but little. A consideration of the above figures makes it evident that during the last few years, the composition of our population from the standpoint of age has undergone a marked change and that we are rapidly becoming a nation of older people. Another factor that is bringing about an increase in our population of individuals of older age is the steadily declining birth rate. It is estimated that the birth rate in the United States in 1900 was 30 per 1,000; 15 years later it had fallen to 25 and it is said to be little if any over 16 per 1,000 at the present time.

A study of the age composition of the population of this country for the last 100 years further emphasizes this tendency to an increase in the older element of the population. In 1850, 52.5 per cent of the total population was under 20 years of age. Each census from then on showed that this percentage dropped. By 1900 it had fallen to 44.4. This had dropped by 1930 to 38.8 per cent and the most recent estimates indicate that only 36.7 per cent of the total population is under 20 years of age. Throughout these same periods, a proportionate increase has occurred among those aged 65 years or more. Less than 100 years ago they made up only 2.6 per cent of the total population. By 1930 this figure had doubled and it is now estimated that they make up about 6 per cent of the total population. During this period the percentage of the population aged between 20 and 40 years has remained virtually constant. The effect of these changes has been to bring about a startling increase in the number of older people, a situation fraught with far-reaching possibilities for our social, economic and political life. In short, the aging process with

its varied and perplexing problems has now become a vital issue in our national life.

Old age is essentially a biological problem. Its better understanding depends upon a clearer conception of the fundamental processes involved. Is aging to be regarded as a physiological involutionary phenomenon or is it disease? This differentiation is not easy and has challenged the best of philosophical and biological thought. The most logical scientific answer to this question is to be found in the delightful essay on Old Age written by the late Aldred Scott Warthin which was delivered in part before this Academy over a decade ago\*. After pointing out that living organisms are destined to pass through the periods of evolution, maturity and involution, he shows that from the moment the ovum is fertilized throughout the entire period of development up to maturity, involutionary changes are taking place along with those of growth. In this way, structures that are no longer of service to the animal economy disappear. The tissue changes that are characteristic of these involutionary processes throughout life are in no way different from those that mark the involutionary changes of old age. From embryonic life until death, therefore, the processes of involution are active and at whatever period they are met and wherever encountered they are identical and consist of the following primary tissue changes:

1. Numerical atrophy—loss of power of cell division.
2. Quantitative atrophy—reduction in size and number of parenchymatous cells.
3. Shrinking and condensation of intercellular substance.
4. Vascular changes—vessel collapse and obliteration of lumen.

These are regarded by Warthin as the primary tissue changes of senescence; changes which are inherent in the organism, which are inevitable and physiologic and, if undisturbed by environmental factors or disease, ultimately lead to failure of vital functions and "biologic death." It is given to few individuals thus to die naturally, because upon these primary involutionary processes secondary pathologic conditions develop, the result of unfavorable environment or inherent cellular defects. These pathologic states have been grouped under changes secondary to vascular lesions such as thrombosis, embolism, hemorrhage, arteriosclerosis; those secondary to atrophy which causes functional failure of

\* The Pathology of The Aging Process, *Bull. New York Acad. Med.*, 1928, 4: 1006.

organs especially the endocrine and nervous system; and changes the result of stasis due to obstruction and resultant infection. It is these secondary conditions that lead to "pathologic death" which may occur at any period of life and which is usually responsible for preventing individuals attaining their life span.

The adoption of Warthin's conception not only furnishes one with a theory of old age based upon sound biologic principles but satisfactorily disposes of the many ingenious hypotheses that have been advanced to explain senescence as a progressive disease. For example, Brown-Séquard believed it to be due to vascular sclerosis; Victor Horsley held old age was the result of degeneration of the thyroid gland; while Lorand implicated all of the ductless glands. Metchnikoff's belief that intestinal putrefaction is the cause of old age has been widely discussed. Carrel undertook to explain the process on the basis of physiochemical changes in the blood serum which becomes senescent. In spite of the various mechanisms suggested, as Warthin has pointed out, these and other modern views on aging are fundamentally in agreement that old age is due to loss of growth energy on the part of the cells and when involution exceeds evolution, atrophies, both qualitative and quantitative, inevitably occur, with resulting functional failures.

Justification for an inquiry into the mechanism of aging is the desire to solve some of the inexplicable variations in the process that are encountered. It is a common observation that the rate of aging is inconstant and differs widely in individuals. There are those who before they reach 60, an age arbitrarily adopted by many students of the subject as the time when senescence may be said to begin, exhibit the physical and mental characteristics of advanced years. In contrast to these prematurely old, are individuals long past their biblical allotment of life who are conspicuous because of their vigor and alert mentality. Although admittedly in the minority, many outstanding examples may be cited of men and women whose old age was marked by their greatest creative achievements. Benjamin Franklin successfully directed the affairs of the State of Pennsylvania at 79. W. H. Welch, who lived to be 80, was active in medical education and research until he died. Goethe was 80 when he completed *Faust*. Between his 70th and 80th years, Thomas A. Edison introduced some of his greatest inventions. Elihu Root, who died at 98, was actively interested in public affairs after he was 90. Oliver Wendell Holmes began to write "Over the Tea Cups" at 80. At 98



Titian painted a masterpiece. Lord Balfour returned to an active political career at 72. Even after 85, Verdi wrote some of his best music. Innumerable similar instances could be drawn from the world's history. What is it that determines this variation in the rate and manifestations of aging? Heredity undoubtedly plays a prominent role. There are some who enter the declining years of life better endowed than others. Serious consideration, however, must be given to adequate nutrition in youth leading to optimal growth and development. Environmental factors such as fatigue, overwork, trauma, infections and intoxications leave their mark upon the individual. In addition to these biological aspects, social, cultural, economic and psychological influences are of an importance as yet not fully understood.

For the most part, the course of normal old age is modified by pathological changes and these in turn are largely the result of those diseases which fall within the category of the degenerative conditions, such as: chronic heart disease, chronic nephritis, arteriosclerosis, angina pectoris, cerebral hemorrhage, diabetes mellitus, cancer and numerous other conditions of like nature. Christian has pointed out that the diseases which play such an important role among older people thus far have been little if at all affected by the advances in preventive medicine and belong to the group of non-preventable diseases. A study of the principal causes of death during the past four decades shows that the rate per 100,000 for the non-preventable diseases has steadily risen, whereas there has been a striking mortality decline in preventable diseases. With this decline, has occurred an extension of life expectancy at birth which in 1800 was around 35 years, by 1900 had reached about 50 years and now is over 61 years. Further analysis shows that this increase in life expectancy is largely the result of eliminating preventable diseases among the younger age groups. In other words, preventive medicine has saved life chiefly among the young, thus enabling them to attain older years and become the victims of degenerative conditions in the end. In short, preventive medicine, by saving the young has materially increased the number of old people in our nation. This explains why heart disease, which was 4th among the causes of death in 1900, now holds first place; why cancer, which 40 years ago was 9th, is now 2nd; why nephritis has risen from 6th to 4th place; vascular cerebral lesions from 8th to 5th; diabetes mellitus from 19th to 10th. On the other hand, tuberculosis, which in 1900 was 1st, has dropped to 6th; diarrhea and enteritis have

fallen to 13th from 3rd; various infectious diseases such as pertussis, diphtheria, measles and typhoid have fallen from 16th, 10th, 14th and 11th places to 21st, 23rd, 24th and 25th respectively. Pneumonia and influenza in a period of 35 years have maintained the same relative positions as causes of death; namely, 3rd and 11th respectively. It is not too much to hope that with the recent advances in chemotherapy these infections heretofore so devastating will soon be found among the less common causes of death.

Although this downward shift in preventable diseases may justly be regarded as one of the triumphs of preventive medicine, it has also helped to bring about this relative increase in older people, who of necessity must suffer more from the degenerative diseases peculiar to later life. This change in the age composition of our population with its attendant increased incidence in the non-preventable diseases is bound to exert a marked influence on medical practice, assuming this trend continues, as in all likelihood it will.

Heretofore, physicians generally have been prone to regard too lightly the infirmities of age and have paid too little attention to disease as it manifests itself in the later decades of life. Such a tendency is not surprising in view of the widespread feeling that the degenerative diseases of the aged are as irremediable as they are inevitable. A changed attitude is essential if the medical needs of our ever-increasing older population are to be dealt with adequately in the future. In the past, the care and protection of youth has been our chief concern. With the steady conquest of an ever-increasing number of preventable diseases, medical care of the young will become less demanding, while correspondingly greater efforts will be required in the management of those who are older. In short, although the importance of pediatrics will not decrease, the importance of geriatrics inevitably must increase.

These changing conditions impose a new obligation upon all who are concerned with the training of physicians. Students should receive special training in geriatrics. They should be taught the altered ways in which diseases manifest themselves in older people. They should learn something of the problems of old age. They should be impressed by the fact that in the decades ahead, no inconsiderable part of their practice will be made up of older people whose special psychology and altered physiology must be understood.

In the future, pediatrics may become more restricted and deal more

with preventive medicine than with the actual treatment of disease. Ample opportunity will, nevertheless, be afforded physicians for the individual care of patients. There will not only be no dearth, but probably an actual increase in patients, the victims of degenerative processes, concerning which more needs to be learned and which provide fertile fields for biologic and medical research.

The symptomatology of the aged has not received the systematic study that it deserves. There are few careful clinical surveys that deal with any considerable group of older people. The most helpful records of complete group-studies on patients aged over 60 years come from the clinic of Dr. Lewellys F. Barker who, in conjunction with his associates, carried out a careful analysis of the more common symptoms of which elderly persons complain and the more outstanding abnormal physical findings in a group of 300 new patients over 60 years old. In this group, 240 were between 60 and 70 years of age. In those that were between 60 and 70, the chief complaints consisted in symptoms referable to: 1. Nervous system, 2. Digestive system, 3. Circulatory system, 4. Locomotor apparatus. There were relatively few whose outstanding symptoms suggested diseases of the respiratory system, the blood, the urogenital tract or the endocrines. In the group that was over 70 years of age, the initial complaints were not dissimilar to those of the younger group.

After these patients had been subjected to a thorough clinical and laboratory survey, a summary of the important diagnostic findings showed that in the age group between 60 and 70, diseases of the cardiovascular apparatus were the most common. The next in order of frequency were disorders of the nervous system, particularly those of a functional character. Diseases of the joints and bones, more especially osteoarthropathy furnished the next most frequent diagnoses. Contrary to what might be expected, in view of the large incidence of chief complaints which were referable to the digestive system, Barker and his associates found in this group only three cases of gall-bladder disease and two cases each of ulcer of the stomach and duodenum. Not surprisingly, oral sepsis was a fairly common finding. Other diagnoses made in this group included eleven cases of tumor, chiefly cancer, five cases of diabetes mellitus, five cases of lues and a few cases of obesity or under-nutrition. In the older group of patients, relatively fewer severe maladies were found. Cardiovascular-renal disease was again predominant. The

incidence of cancer increased. Contrary to expectation, Barker found only four cases of senile psychoses in the entire group of 300 patients. In the main, the above analysis bears out the impression of most clinicians as to the distribution of the more serious diseases of the aged.

There is no more important aspect of senescence than the psychological and sociological ones. Old people present certain psychological phenomena peculiar unto them which must be thoroughly understood and appreciated if the problem of old age, both from an individual and a collective standpoint, is to be successfully handled. The prospect of old age does not appeal to most people. One's attitude towards growing old differs at various age periods. To the younger individual, the possibility receives scant consideration. In mature adult life, when old age is no longer remote, there are many who refuse to take a realistic view of the situation and shrink from all discussion of the problems of senility and death. It is not until the individual has actually attained old age that there is any degree of reconciliation to the restrictions of the advancing years and the relative proximity of death. Even then, there are many who are resentful of their infirmities and are unwilling to contemplate the inevitable with the calm philosophy that should characterize the psychology of the normal aged.

Those who have attempted to evaluate the view points of older people agree that it is not death that is feared by them so much as the dread of chronic invalidism and economic and social dependence—the thought of no longer being necessary and of losing a position of dominance whether that be in the family, industry or profession. A feeling of inadequacy may be said to be a prominent psychic burden of most old people. It is the common experience of every clinician that many older people suffer distressing unhappiness because of their unwillingness to accept their declining physical, mental and sexual powers with equanimity. They are reluctant to admit that age is robbing them of their ability to accomplish and to dominate as they formerly did and they try to blame their handicaps on failing health and various unfavorable environmental factors rather than on their declining years. Much of this psychology arises from the desire of people to regain their lost youth. They are not content with the prospect of a dignified, orderly, comfortable decline. Like Ponce de Leon of old, what they really seek is some “fountain of eternal youth.” Hence, the abortive and ironical efforts at rejuvenation that from time to time have gained popularity in spite of

the fact that, viewed in the light of the pathology of old age, they are doomed to failure from the start. When we add to these psychological tribulations of growing old, the fear of economic insecurity, it is small wonder that senescence is not anticipated with enthusiasm.

Many of these factors so disturbing to the tranquility of the aged could be offset by the proper psychological handling of the individual. This brings the problem squarely before the physicians and immediate families responsible for the direction of the lives of the aged. Nothing is more disastrous or creates a worse psychic shock to aging people than a termination of their active interest. In all examples of successful and creative senescence to which reference has already been made, the common denominator is apparent; namely, a continuation of interest. When interest in some phase of life, be it profitable or otherwise, ceases, the burden of old age becomes heavier. For that reason, we, as physicians, should exercise our ingenuity in devising ways and means of keeping our older patients occupied. It is not sufficient to keep up the interest of the aged—what many seek most is a sympathetic understanding of their problem, particularly on the part of those with whom they live. The fact that an individual has undergone certain psychic changes, as the result of advancing years, does not alter the fact that he or she still is capable of emotional and sentimental reactions. Too often the needs of the aged in this respect are sadly neglected.

In spite of the trials which beset old age, it is not entirely without its compensations. To the healthy aged, especially if they can enjoy a certain financial independence, come freedom from responsibility and relief from the strain of competition. This brings increased leisure which enables them to pursue many activities and interests for which there was never time during their years of industrial or professional activity. They may live where and how they wish, no longer being forced to make their lives conform to the exigencies of their work. Long-neglected interest in cultural and civic problems may now receive their attention. The experiences gained in the course of an active life have adjusted their perspective and have given them mature judgment. Best of all, with aging has come conservatism. The prejudices and partisan fire of youth have given place to forbearance and tolerance. These are distinct assets, the views of the impetuous younger generation of our day notwithstanding—assets which should not be wasted but used and capitalized by Society, which with advantage might well hearken to the voice of experience.

There are definite political potentialities inherent in this conservatism of older people. The steady increase in the older group of our population has already been stressed. It is admitted that conservatism increases with age. As Professor John Dewey puts it, "In the degree in which the older group expresses itself politically we have the curious and indeed ironical condition that at just the time when measures of social readjustment are most needed, there is an increasing number of those whose habits of mind and action incline them to resist policies of social readjustment."

The deprivations and limitations of old age are by no means entirely biological. They are quite as much the result of the social order which we have developed. In a Society that has come to exalt economic success and to idealize youth, old age is regarded as a liability rather than a distinction. Traditions which developed with the frontier spirit when over one-half of the population was under 20 years of age still dominate national thought. The flagging powers of advancing years are stressed on every hand and as individuals approach middle life they are made ever mindful of the fact that their initiative, adaptability and creative ability are failing; they are no longer efficient; in short, that they are growing old. Soon they become aware that on every hand, opportunity is closed to them, that they must give away before the rising tide of youth. Then with the full realization that in the modern economic and social structure, there is no demand for their ripe experience, they yield to a sense of frustration and prepare to accept retirement as their lot.

This popular attitude concerning old age has been accepted by many professions and industries in which age limits have been placed upon employment, even though there is no scientific proof that hard work *per se* ever wears out healthy men and women. Inactivity leads to our undoing; activity keeps us alive. The worst shock that can come to any one is to be retired, particularly if that retirement is to make place for some one younger. Even those who are mentally alert and vigorous, when they are forced out of the activities of life in which they have so long played an important part, become old, often with incredible rapidity. Responsibility and duty serve as a stimulus to activity and interest. When they are removed, the urge to effort ceases and the characteristics of old age supervene. It is the exceptional individual who is able to function usefully in retirement. As a rule, the only people who profit from retirement are those who have developed interests aside from their business or profession and who have been able to plan and prepare systemat-

ically for their period of withdrawal from active work. Every physician of experience will subscribe to the statement of Roy Helton: "A sudden loss of sustaining habits and motives that have kept him in active competition for the rewards of labor, can within 6 months transform the busy lawyer, physician or merchant into an aged hypochondriac." There is nothing so devastating to the self-respect and pride of any man as to find himself forced by retirement out of his active part in the affairs of life. To one who has enjoyed well-earned independence and walked with his head high among men, the abrupt assumption of a role of dependency, whether it be upon his family or the State, brings about a sense of uselessness and a retreat into the past.

The question of retirement from active employment is closely interwoven with the far-reaching economic and political aspects of the problem of aging. The falling birth rate in this country, the relative decrease in children under 5 years of age in the last three-fourths of a century, and the fact that the relative number of persons over 65 has almost doubled in this period have already been noted. In the meantime, the productive population aged 20 to 44, the age level of active employment, has remained constant. Obviously this is the group upon which falls the chief burden of caring for the young and the dependent older people. As child-labor legislation and more years devoted to education diminish the number of young workers, and enforced earlier retirement is diminishing the number of older workers, the group of productive workers grows smaller. Increasing responsibility falls upon them, because they must provide for the young, an actually increasing group of older people steadily being augmented by those who are retired, as well as the unemployed. Thus we find a minority group of producers subjected to the economic strain of caring for all the rest. In order to relieve individuals of this increasing burden, the government assumes, in part at least, this responsibility, but this "social security" can be provided only by increased taxation which in turn falls almost to a confiscatory degree upon the industries of the country which employ labor. Thus a vicious cycle creates a wholly unbalanced situation.

As a result of a discussion of old age pensions, one of the well-known columnists, Mark Sullivan, presents some startling figures of far-reaching implication. Under the caption, "Forty Million Workers Must Support 116,000,000 Others in 1965", he proceeds to state that, according to the conclusions of several experts, 25 years from now the total population

of the United States will be about 157,000,000 as compared to the present of about 133,000,000. Although this increase in total population is comparatively small, the important point is that the increase in the number of old people will be rapid and great. Those aged over 65 years will have increased from 46,000,000 to 60,000,000. Meanwhile, the number of productive workers aged between 20 and 65 will have remained about as now, around 80,000,000.

The first thing to notice, for its bearing on old age pension plans, is the doubling of the number of old folks. The second thing to notice is the material increase in the number of young folks. The third thing to notice is that the number at working age will remain about the same. For this last class, the prospect is disturbing; for they must support either privately or through taxation, the other two classes.

The working group must pay for the schools for the young and the pensions for the old and the combined number of old and young will have increased from 54,000,000 to 76,000,000, while the number of workers will not have increased, but will remain at about 80,000,000. Actually, the number of workers is not 80,000,000; about half of these are housewives or are otherwise not employed. Actually, about 40,000,000 workers will be supporting an equal number of their own age, about 60,000,000 young, plus 16,000,000 old, or a total of 116,000,000. In other words, two groups, the old and young, will be looking to the working group for support. Politically, the old will have two votes; the young will not.

The potentialities of such a situation, politically and economically are suggestive if not disconcerting. It has been suggested that one way to take political control from premature senility is to legislate the vote away from the old as we already do from the young. This would reduce the pressure block of the old to equality with the young. If the situation is allowed to exist undisturbed, consequences, in the judgment of experts, of an unpredictable and even revolutionary character may result. Speculations include a new kind of class war, a kind of political civil war between young and old; and another war, with young and old combined on one side and the workers on the other. Certainly there will be many consequences, having ramifications into every phase of life.

It is hard to visualize a more disastrous situation for any people than to allow their politics to come under the control of an idle old age group living without labor upon the bounty of the State or private enterprise.



As Helton has remarked with timely emphasis: "It will not be safe for America to permit the present psychology of old age to dominate even a powerful minority of our citizens." Four years ago we witnessed political campaigns based upon promises of financial assistance to the aged. For the most part they failed. Unless conditions are altered, similar efforts a decade from now may well meet with success, since the older group will have gained in numbers and political power.

What is the solution of the complicated problem presented by the steadily increasing group of the aging? They have been taught to believe that all they need is money. That alone is far from the answer to their difficulties. The inexorable laws of nature coupled with the trends of the social order we have built have brought to old age unhappiness and tragedy. This unhappiness is not entirely economic, it is primarily due to the inadequacies and maladjustments inherent in the old. That they often need money and are entitled to adequate support is axiomatic. The responsibility of Society to them goes further and involves a thorough and complete study, carried out with scientific detachment, of the needs of old age. Such a survey requires the intelligent coöperation of physicians, psychologists, psychiatrists and sociologists.

If we wish to alleviate the condition of the aged, the first step is to educate people to plan and to provide for their old age. Those who, through their own foresight, have established a certain degree of economic independence can approach the other aspects of growing old with more happiness and equanimity than the less fortunate. The pensions which have been contemplated or, as the result of legislation, are in effect, will doubtless mitigate to some extent the needs of the poor, but are wholly inadequate to maintain most older people at the social and economic level to which they have become accustomed. The aged have become or have been made acutely conscious of their incapacities and, as the result, have accepted the principle of retirement with little protest. Instead of expending their efforts in organizations designed to obtain for them a dole, it would be far more profitable for them and, at the same time, for the community, if they were aroused to the importance of combating in some effective manner, compulsory retirement. The greatest insurance for happiness at any age lies in work. There is no better outlet than to continue with the work which one has carried on throughout the greater portion of one's life. It is agreed that, because of their failing powers, it is inexpedient to demand of old people that they carry on

their maximal activities throughout life. It would seem possible, however, that in industries and professions an individual's work might be modified to meet his or her restrictions, thus permitting continued interest and active part in their accustomed occupations.

It is a fallacy to assume that older people no longer retain a capacity to learn; many seek opportunities for further study. Some extension of our educational system which would enable the older people who are mentally equipped, to seek diversion in further education would be desirable.

The aged in our midst must be impressed with the fact that, although Society is willing and eager to make every reasonable provision for their security and happiness, they must not acquire the attitude of accepting such succor passively but must put forth a constructive effort to help themselves. In the past, the mistake has been that older people have endeavored to compete with youth. Such an attempt must inevitably fail. They should be stimulated to develop interests and to occupy themselves within their capacities. They would profit by contacts and associations with those of their own age group. When we can offer those of older age opportunities for occupation and have imbued them with the idea of self-sustaining activities they will lose some of their willingness to sink into a parasitic existence.

In the foregoing, an effort has been made to show that the increasing number of older people in the nation presents a definite problem. A problem which if great today, will be far greater tomorrow. The issue is inescapable and must be met with frankness and fortitude. Its solution will require not only the best economic thought and political sagacity but also the sincere and whole-hearted coöperation of medicine and the biologic sciences.

## HISTAMINASE: PHYSIOLOGIC EFFECTS ON MAN AND ITS THERAPEUTIC VALUE IN MEDICINE\*

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HISTAMINASE is the name designated by Best and McHenry<sup>1,2</sup> for an enzyme-like substance which destroys histamine in the body of an animal. While Eustis<sup>3</sup> in 1915, working on the livers of turkey buzzards, first suggested that some enzyme might exist in the body which would inactivate histamine, it was not until 1930 that Best and McHenry isolated such a substance as a stable dry powder from beef kidneys. By means of perfusion experiments in animals, histaminase was found in relatively large amounts in the kidneys and large and small intestine and in moderate to small amounts in the other tissues of the body except the liver. However, in 1935, Steggerda, Essex and Mann,<sup>4</sup> using perfusion experiments in dogs, found that the amounts of histaminase in the liver were smaller than those in the kidneys but greater than those in other tissues they examined.

Although Best and McHenry had demonstrated the existence of histaminase in 1930, no apparent effort was made toward the clinical preparation or use of such a substance until some years later. In 1936 an intestinal mucosal extract which had properties said to be similar to those of the histaminase of Best and McHenry was introduced into this country from Germany. At that particular time we were especially interested in patients with hypersensitiveness to cold. If the liberation of histamine or a histamine-like substance, as had been suspected, was the causative agent in the pathogenesis of hypersensitiveness to cold, then this intestinal mucosal extract, histaminase, should be effective as a method of treatment in this condition. Therefore, the use of histaminase was begun in cases of hypersensitiveness to cold.

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While this work was being carried on in this country, reports of the use of histaminase in the treatment of various so-called allergic conditions began to appear in the same year in Germany.

Although we have studied the effects of histaminase in this country since 1936, it is only since its preparation in this country during the last nine months that adequate supplies of a well standardized preparation have been available for use in any large group of cases.\* Both the physiologic and the clinical results are, therefore, preliminary in nature.

In order to determine in which clinical conditions the histaminase might be most useful and to attempt to evaluate the physiologic action of histaminase, it is necessary to review in part some of the work and some of the difficulties involved in the study of the physiologic reactions of histamine.

Since the isolation of histamine from ergot in 1910,<sup>5</sup> and from animal intestinal mucosa in 1911, by Barger and Dale,<sup>6</sup> the study of its effects on animals and man has formed the basis for many diversified investigations. The difficulty of isolating histamine quantitatively in crystalline<sup>7,8</sup> form from animal tissues and blood has been an obstacle in most of these studies. Many investigators have attempted to devise a suitable method for this purpose, but as yet, for the most part, the final analysis in the determination of histamine is still concerned with biologic assay.

Furthermore, inability to isolate histamine in its crystalline form has given rise to various names, such as H-substance, histamine-like substance and histamine-yielding substance, for those substances which produce histamine-like reactions physiologically. In most instances the parallelism between the responses of histamine and histamine-like substance is so apparent that, if one reviews the literature and observes the various responses, it is difficult to determine wherein they differ.

Histamine reactions in man may be divided into systemic and local skin reactions. The systemic reactions following the parenteral administration of histamine are characterized by a decrease in blood pressure, an increase in pulse rate simultaneous with marked flushing of the face, a rather intense headache and a subsequent rise in the gastric acidity.

In this paper it will be possible to mention only a few of the excellent investigations that have been made on the local skin reactions.

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\* Histaminase was kindly supplied for this work by the Medical Research Department of the Winthrop Chemical Company as Histaminase and Terantil.

In 1913 Eppinger and Gutmann<sup>9</sup> in Germany noted the effects produced by intradermal injection of histamine and in 1912 Eustis<sup>10</sup> in this country stated the similarity of urticarial lesions to the reactions produced by intradermal application of histamine. He expressed the opinion that histamine is concerned with the production of urticaria.

The most comprehensive studies of the local skin reactions were made by Lewis and Grant<sup>11</sup> in 1924 and Lewis, Grant and Marvin<sup>12</sup> in 1927. They showed in cases of dermatographia or urticaria factitia that the reactions to stroking of the skin in these subjects and the reactions from the intradermal injections of histamine in the same individuals were strikingly similar. Lewis has shown that the simultaneous production of wheals at various points on the skin of a subject with factitious urticaria may produce a flushing of the face similar in every respect to that obtained after the subcutaneous injection of histamine. They expressed the opinion that the liberation of histamine or of H-substance is probably the causative factor of the reactions. In these subjects, mechanical, electric, thermal and chemical stimulation produced the so-called triple response. They also observed that the increased permeability of the blood vessels of the skin was followed by a peculiar condition of partial or complete refractoriness to further stimulations of the same kind. As this condition of refractoriness became established, the increased permeability of the blood vessels of the skin disappeared. The development of a state of refractoriness by repeated, increasing doses of histamine in the intact animal had been demonstrated by Fühner<sup>13</sup> and Oehme<sup>14</sup> in 1912 and 1913. All these observations made possible a method of treatment later in clinical conditions.

The investigations concerned with the systemic effects of histamine are so varied and comprehensive that it would be impossible to include even a goodly number of them in this paper, but a consideration of one of the clinical phases seems logical at this point.

Urticaria attributable to cold was recognized as early as 1866 by Bourdon,<sup>15</sup> but it was not until 1872 that Blachez<sup>16</sup> gave the first classic description of this phenomenon. During the next fifty years various single reports were published on urticaria produced by exposure to cold, for the most part with only local manifestations, but in a few instances cases such as the one described by Duke<sup>17</sup> in 1924 were reported, in which urticarial eruption and a severe constitutional reaction occurred.

In 1927<sup>18</sup> and 1929<sup>19</sup> one of us (Horton) and Brown reported six

cases of hypersensitiveness to cold in which local and systemic reactions were so striking as to constitute a clinical entity. They were able to reproduce the local and systemic reactions by immersion of one hand in water at 8 to 10°C. for a period of six minutes. The local effects on the skin consisted of pallor during the period of exposure, followed by redness, swelling and increased local temperature on removal of the hand or exposed part from the cold water. After a latent period of from three to six minutes a characteristic systemic reaction developed, consisting of flushing of the face, a sharp fall in blood pressure, a rise in pulse rate, and in some instances a development of syncope.

When a tourniquet was applied to the arm for seven minutes while the hand was immersed in water at 10°C. and kept on for an additional eight minutes after the hand had been removed from the water, no local or general reaction occurred until the tourniquet was removed. This observation was important, for it ruled out the possibility of a reflex basis for the systemic reaction.

In addition they were able to reproduce the clinical syndrome by the subcutaneous administration of 0.5 mg. of histamine to the patient. They suggested that a physical agent such as cold might allow the release of a sufficient amount of this substance to produce both the urticarial response and the general systemic reaction. Because of the work previously mentioned on the development of a state of refractoriness from repeated, increasing doses of histamine, one of us (Horton) and Brown suggested that since the patient was sensitive to a chemical substance formed in the tissues, probably histamine, passive desensitization by repeated injections of histamine over long periods in minute doses, which were insufficient to produce a systemic effect, and gradual increase in the doses should prove an effective treatment and that probably the same should be true of repeated immersions of the hand in cold water. They were able to prevent both the systemic and the local reactions of various patients by means of immersion of one hand in water slightly above 10°C. for from one to two minutes twice a day for from three to four weeks or by means of subcutaneous injection of 0.1 mg. or less of histamine, twice daily for from two to three weeks. The treatment with histamine was confirmed by Bray<sup>20</sup> in 1932. In further work in 1932 one of us (Horton) and Brown,<sup>21</sup> by immersion in water at 10°C. of one hand of each of several patients who were hypersensitive to cold, produced a rise and fall of gastric acidity identical with that

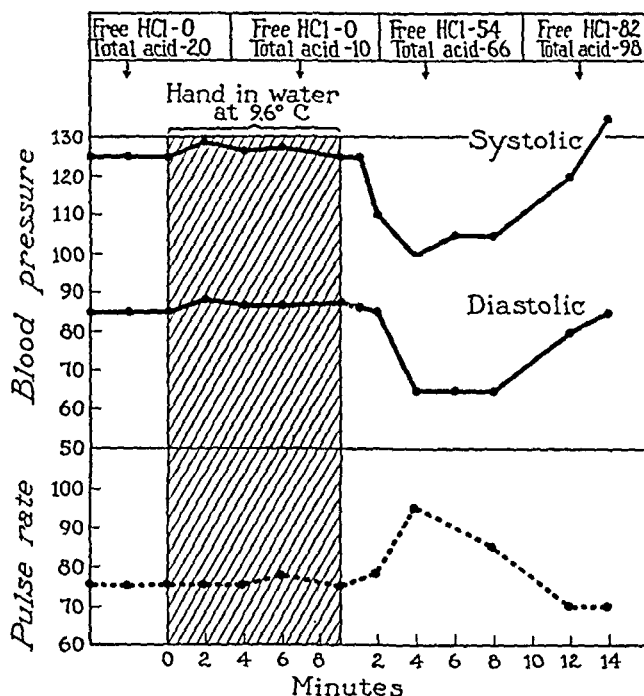


Fig. 1. Typical changes in blood pressure, pulse rate and gastric acidity in a case of hypersensitiveness to cold following immersion of one hand in water for nine minutes.

noted after parenteral administration of histamine (Fig. 1).

In 1936 the clinical and experimental investigation of twenty-two such cases was summarized.<sup>22</sup> These patients, eleven women and eleven men whose ages ranged from fifteen to fifty-nine years, exhibited abnormal local and systemic reactions following exposure to cold. Symptoms had been present for from one month to thirty years and consisted for the most part of urticarial wheals over the face, neck and hands and occasionally over the feet, thighs and trunk. Urticarial manifestations invariably followed exposure to cold wind, cold water or a cold environment. A number of the patients had swelling of the lips and one had dysphagia following ingestion of cold water or ice cream. Nine of the subjects had collapsed after swimming and four of them had to be rescued from the water. In sixteen of the twenty-two cases, the attacks were prevented by desensitization to cold or to histamine.

Histaminase has been given to ten patients with hypersensitiveness to cold. In all instances we reproduced the syndrome by immersion of one hand in water at 10°C. for seven minutes. Following administration

of histaminase for a number of days, the hand was again immersed in water at the same temperature and for the same period of time; at this time both the systemic and local reactions were slight or did not occur at all.

In some instances where the gastric acidity<sup>23</sup> was determined before and after administration of histaminase, the resulting figures showed a marked decrease in the rise of the gastric acids in the second test.

Because of this effect on gastric acidity, it was felt that further studies of gastric acidity should be made. Accordingly, studies were made with Gabrielsen<sup>24</sup> concerning the effect on the gastric acidity of five normal subjects when their whole body was immersed in water for fifteen minutes, the baths ranging in temperature, with intervals of 5°F. from 65° to 100°F. (18° to 38°C.). The gastric samples were obtained before the subject was immersed, at the end of fifteen minutes just before the subject was removed from the bath, and at fifteen and thirty minute periods after the subject was removed from the bath. While there was little or no rise in the concentration of the gastric acidity fifteen minutes after the immersion of the subject in water at body temperature or above, a rather definite rise in the concentration of gastric acidity occurred particularly fifteen minutes after the removal of the subject from water ranging from 65° to 85°F. (18° to 29°C.).

At a temperature of 75°F. (24°C.) there was no visible shivering and in an attempt to determine whether this rise in gastric acidity was due to an increase in metabolism, the basal metabolic rates were determined in one subject before and at the height of the rise. At those periods no change in basal metabolic rate was noted. At present we are carrying out further work in regard to this study. In order to determine whether this response of the gastric acidity of normal subjects fifteen minutes after immersion in water at 75°F. (24°C.) was a histamine or a histamine-like reaction, histaminase was tried. Commercially available histaminase is obtained from the intestinal mucosa and the kidney, and the oral preparation is enteric coated. Consequently it is probable that absorption only takes place after it reaches the intestine. Therefore, a special preparation was obtained which consisted of a fine white powder that could be suspended in physiologic saline solution and administered by means of the duodenal tube. We found in these five normal subjects that the introduction of histaminase into the duodenum by means of the duodenal tube thirty minutes before the subject was immersed in water



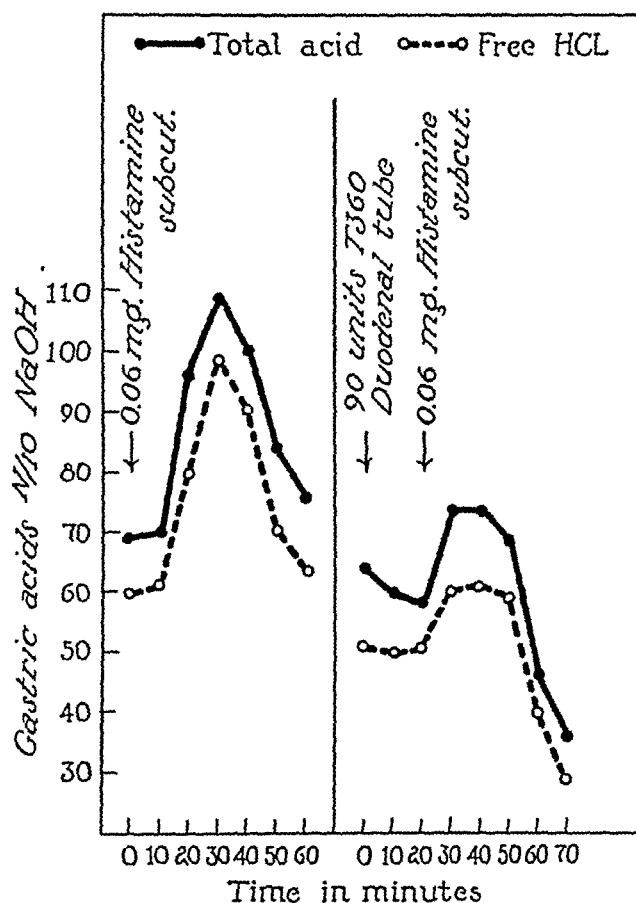


Fig. 2. Response of gastric acidity to subcutaneous injection of histamine. Response of gastric acidity after introduction into the duodenum of 90 units of histaminase (T360), preceding injection of the same amount of histamine thirty minutes later.

at 75°F. (24°C.) could inhibit the rise in gastric acidity produced by immersion of the subject in water at that temperature. Control studies were made with the introduction of physiologic saline solution into the duodenum.

Following these observations the normal response of the gastric acidity to subcutaneous injection of 0.06 mg. of histamine was determined. Several days after this response was accurately established, histaminase was introduced into the duodenum twenty-five to thirty minutes before subcutaneous injection of histamine. In this small series, following the introduction of the histaminase, the rise of gastric acidity was rather definitely decreased (Fig. 2).

In addition, again after the normal response to the subcutaneous injection of 0.06 mg. of histamine had been determined, a parenteral preparation of histaminase was injected intramuscularly thirty minutes before the usual subcutaneous injection of histamine. Again the rise in gastric acidity was decreased but was not completely inhibited except in two instances.

Furthermore, following the administration of histaminase by duodenal tube or intramuscular injection, the other systemic effects produced by administration of histamine, such as flushing of the face, decrease in blood pressure and increase in pulse rate, were practically abolished.

While the preparation, dosage and time may not have been optimal and the investigative work is incomplete and further studies are being carried out, these observations would seem to indicate that histaminase administered to man can inhibit the action of histamine or a histamine-like substance. The mechanism by which this is accomplished is unknown to us.

Since the use of histaminase seemed effective in the cases of hypersensitiveness to cold, in which we could produce the syndrome and note the results with considerable accuracy, further use of histaminase in other clinical conditions where histamine or a histamine-like substance might be a factor seemed feasible.

#### HEADACHES

Erythromelalgia of the head (histaminic cephalalgia) is a new clinical syndrome which was first described by one of us (Horton), MacLean and Craig<sup>25</sup> a year ago. It is characterized by unilateral headache which is sudden in its onset and excruciating in character and usually involves the neck, face, temple and eye. The distribution of pain does not follow that of any of the cranial nerves. There is almost invariably evidence of congestion about the involved eye and lacerimation is a prominent feature. Unilateral obstruction of the nose is frequently present during the attack. The patients have had none of the tic-like symptoms of trigeminal neuralgia and no trigger zones have been demonstrated. In contrast to the typical migraine headache, these patients do not have a hereditary incidence or an early history of migraine. There are no scotomatous or gastrointestinal accompaniments. These patients have found no relief from the usual methods of treatment.

These vasodilating headaches have been induced at will by the administration of histamine. Furthermore, treatment by "desensitization" with histamine has been previously carried out in a fairly large number of cases and has been previously reported. In view of the fact that we were able to induce these attacks at will by the subcutaneous administration of small amounts of histamine (0.1 to 1 mg.), it seemed logical to try out the use of histaminase in a group of these cases to see if good results could be obtained. Only a limited number of patients have been studied in this manner. However, in practically every instance where the patient has had the syndrome of "erythromelalgia of the head" these attacks have been eradicated by the use of histaminase. Not only do we feel that "desensitization" with histamine is a specific treatment for "erythromelalgia of the head," but our recent observations with the use of histaminase lead us to believe that it is almost as effective as "desensitization" with histamine. Further studies are being carried out.

#### SERUM SICKNESS

Following our report on the effects of histaminase on patients with hypersensitiveness to cold, Foshay and Hagebusch<sup>26</sup> in 1939 reported the use of histaminase in the treatment of serum sickness. They found that the administration of histaminase, either orally or intramuscularly, brought marked relief to twenty of twenty-two unselected patients with serum sickness, most of them with the severe forms of the disorder. Eighteen patients were treated on either the first or the second day of illness, and sixteen obtained marked relief in from eighteen to thirty-six hours. Foshay and Hagebusch felt that the prophylactic use of the substance would prevent the occurrence of serum sickness in some instances and ameliorate the severity in others.

Cherry and Prickman<sup>27</sup> have reported an additional twenty-two patients who received histaminase in the prevention and treatment of serum sickness. The majority of their patients were treated for lacerations and compound fractures and were given routinely either tetanus antitoxin or the combined tetanus and gas gangrene antitoxin as a matter of prophylactic protection. Histaminase was administered to eight additional patients who received a variety of horse serums such as antistreptococcic serum, bacillary dysentery serum, and so forth. This group added to Cherry and Prickman's group made a total of thirty patients.

The effects of histaminase, generally from thirty to forty-five units

daily, were observed after well-developed serum sickness. Relief was observed in fourteen of seventeen cases in eighteen to thirty-six hours, and no relief was noted in three cases. When administration of histaminase and serum was started simultaneously because of positive patch skin tests or a history of allergy in thirteen cases, no serum sickness occurred in eight cases. In three cases a transient urticaria appeared which disappeared in twenty-four hours. In most instances this was due to the discontinuance of the drug on the seventh day which should have been continued through the tenth to twelfth day as the delayed serum sickness does not often occur until the seventh day. Since the urticaria was very mild, there was practically complete relief in eleven of these patients. No relief could be noted in two cases. While the series is small, it compares favorably with the results of Foshay.

#### INSULIN ALLERGY

From the work of Lewis and his co-workers, histamine or a histamine-like substance was thought to be a contributing factor in a group of local skin reactions to subcutaneous injections of insulin and various horse serums. Hence, a study of the treatment of local skin reactions to injections of insulin was made by one of us (Roth) and Rynearson.<sup>28</sup> It had been noted that many patients experienced a mild local reaction to insulin when it was first administered. These mild reactions usually disappeared within one to two weeks.

However, this study deals only with cases of long duration in which there were very annoying skin reactions to insulin. At the site of each injection of insulin an area of from 2 to 6 inches (5 to 15 cm.) in diameter, which is red, raised, hard, tender and itchy, develops and may persist for several days.

The incidence of skin reactions among patients who are receiving insulin varies in different reported series. Collens, Lerner and Fialka<sup>29</sup> reported an incidence of 7.3 per cent, Allan and Scherer<sup>30,31</sup> of 15.1 per cent and Lawrence<sup>32</sup> of 30 per cent.

Many types of treatment have been tried for these local reactions to insulin, including change of the type of insulin, desensitization with very small amounts of insulin<sup>33</sup> injected intradermally and desensitization with small amounts of histamine. In one instance, Karr, Scull and Petty<sup>34</sup> sensitized a rabbit to the patient's serum and then gave the patient the active serum of the rabbit. The allergic reactions disappeared.

Forty-five to sixty units of histaminase were administered orally each day to each of twelve patients with this type of local insulin allergy. In ten cases daily injections of insulin could be given without local skin reactions in from two to ten days after the administration of histaminase was begun.

#### LOCAL SKIN REACTIONS TO SUBCUTANEOUS INJECTIONS OF ANTISTREPTOCOCCIC SERUM

Another group of thirty cases in which similar annoying local skin reactions persistently developed after injections of antistreptococcic horse serum was studied. The reactions consisted of areas of from 2 to 5 inches (5 to 13 cm.) in diameter at the site of injection which were red, raised, hard, tender and itchy. These areas generally persisted for four to five days. Histaminase was administered orally to these thirty patients after definite soreness and itching were developed. A history of allergic manifestations was obtained in nine cases and, when positive skin patch tests with the various antistreptococcic horse serums were made, positive skin reactions to these patch tests were obtained in twenty-seven of the thirty cases. In the other three, soreness and itching at the site of injection were noted only after the concentration of the injected serum had been increased. In thirteen of the cases local reactions were prevented in two to four days by 45 to 60 units of histaminase administered orally, and the patients were able to finish their course of serum treatment. In six cases there was some improvement but not a more rapid disappearance of the local reaction. In eleven of the thirty cases the serum treatment was stopped because of the persistence of the local reaction following each injection. Again this is not a large series and although these results are encouraging, a considerably larger group of cases should be studied.

#### URTICARIA

It has been thought by certain investigators that urticaria may be in some way related to release of histamine or histamine-like substances and on this theoretic basis the use of histaminase seemed logical in cases of urticaria.

In 1939 Laymon and Cumming<sup>35</sup> reported the use of histaminase in seventeen cases of urticaria. They noted a clinical cure in 59 per cent of their patients; 12 per cent were improved and 29 per cent were un-

improved. Because of the small number of patients treated with histaminase and the relatively long duration of the condition, they did not draw any definite conclusions concerning the value of histaminase in the treatment of urticaria.

Forman<sup>36</sup> in a study of ten cases of chronic urticaria demonstrated that histaminase was helpful in the treatment of chronic urticaria except for one case in which more severe hives with nausea and heartburn was produced by the administration of the capsules. It was found that the patient gave skin reactions to cow's milk and beef.

Histaminase was administered to fourteen patients who had urticaria. Where the attacks occurred spontaneously in spite of the elimination of many foods and the presence of no known precipitating factor, almost immediate cessation of development of urticarial lesions was obtained in fourteen to twenty-eight hours. With continued treatment, this relief lasted a period of three weeks while the patients were under observation. One patient has obtained only partial relief. Two patients in whom urticaria developed during pregnancy, remained free from urticaria when 30 units a day were given. When the dose was less than that amount, urticaria reappeared. In five of six cases various drugs, such as liver extract, cobra venom, treparsol and morphine, precipitated attacks. Complete cessation of the development of urticarial lesions was obtained in twelve to forty-eight hours and the lesions did not reappear with the continuance of the various drugs. One patient who had a fourteen year history of asthma obtained only a partial cessation at the end of forty-eight hours. Another patient with giant urticaria of one year's duration was not relieved.

While these effects are interesting and encouraging, we realize that there are a number of types of urticaria and our series is too small to justify any conclusions as to the effects of histaminase in a condition which is characterized by great irregularity in the appearance of the lesions and their spontaneous disappearance.

#### VASOMOTOR RHINITIS

Because certain cases of vasomotor rhinitis are allergic in nature, Prickman, Lillie, Fleming and one of us (Roth)<sup>37</sup> made a study of forty patients with vasomotor rhinitis.

In 1937, Adelsberger<sup>38</sup> reported very favorable results in the treatment with histaminase of eight patients with allergic rhinitis. He stated

that five of these patients were cured, one was improved and two received no benefit.

In our study the nasal membranes were observed before and after histaminase was administered orally. Thirty to 50 units were given three times a day before meals to each of the patients for seven to fourteen days. Eighteen patients were relieved of the nasal obstruction, watery discharge and sneezing; a definite improvement in the appearance of the nasal membranes could be seen. The condition of eight patients was improved but not to the extent experienced by the eighteen previously mentioned. The remaining fourteen patients did not receive appreciable relief. It is interesting that, following the intravenous administration of histamine to patients, numerous attacks of vasomotor rhinitis have been produced.

### SUMMARY

We have presented our physiologic evidence on the relation of histaminase and histamine in man. These observations are limited in number, and the work is far from complete. The development of such studies has been slow and impeded by the lack of a readily available method for quantitative isolation of crystalline histamine from blood and tissues.

We have observed 150 patients with various clinical conditions to whom histaminase has been administered orally. No untoward effects with doses as high as 125 units in a day were noted in any of these patients.

There is evidence to show that histamine or a histamine-like substance is a factor in the pathogenesis of certain clinical disorders characterized by local or general hypersensitiveness and in these clinical disorders histaminase has been used in an effort to inhibit the action of these substances.

From the results of this preliminary report and on the basis of our experience and that of others, histaminase seems to be an effective therapeutic agent in certain cases of clinical hypersensitiveness.

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# THE MEDICAL MANAGEMENT OF DISORDERS OF THE BILIARY TRACT\*

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It is impossible to cover the whole field of management of biliary tract disease in a short period of time, therefore, I shall discuss principally some developments of recent years which have altered materially concepts previously held in regard to diagnosis and treatment. This subject is of great importance because the biliary tract is usually considered to be the most common cause of digestive symptoms (Rehfuss,<sup>1</sup> Mentzer<sup>2</sup>). There are moreover, great differences of opinion as to certain facts: the relative importance of various factors causing biliary tract disease; the types of cases responding best to medical or surgical therapy; the value of various methods of medical treatment. It is to problems of this character that my time will be mainly devoted.

## GENERAL CONSIDERATIONS

*Extra-Hepatic Physiology:* Since an understanding of biliary tract disorders is necessarily based upon a knowledge of normal function, a brief review of biliary tract physiology is justified. The most essential fact, and the one most commonly overlooked, is that the biliary tract as well as the rest of the digestive system is under the direct control of the autonomic nervous system.<sup>3,4</sup> With remarkable consistency, the liver continuously secretes the bile which during fasting is prevented from entering the duodenum by the common duct sphincter of Oddi (Ivy<sup>5</sup>). The dilute hepatic bile is therefore diverted into the gall bladder, which acts not only as a reservoir and equalizer of biliary tract pressure, but also concentrates the bile four to ten times, mainly by the absorption of water (Ravdin<sup>6</sup>). According to most investigators, the concentrated bile is discharged into the duodenum by the more or less simultaneous contraction of the gall bladder and the relaxation of the common duct sphincter (Lyon<sup>7</sup>). This action is instigated by the hormone cholecys-

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tokenen, which is formed in the duodenum as the result of stimulation of food chyme (Ivy<sup>5</sup>). Following the discharge of concentrated bile in response to food, the common duct sphincter again closes and the contracted gall bladder is once more filled with bile.

A study of pressure relations in the biliary tract affords a means of understanding the cause of certain symptoms and functional disturbances. The common duct sphincter is capable of resisting a pressure of 75 cm. of water, whereas the gall bladder is capable of exerting a pressure of only 30 cm. (Ivy<sup>5</sup>). The ways in which normal physiological action may be disturbed by functional disorders, infection, and obstruction will be discussed later.

### FACTORS IN DIAGNOSIS

*The History:* The diagnosis of biliary tract disease depends primarily upon an accurate history, which must include in addition to an account of digestive symptoms, a study of the individual, his personality and environment. It is only by this approach that functional disturbances ultimately may be determined; by the relationship of acute symptoms to emotional disturbances, business or financial worries, unhappy marital relations, or conditions leading to physical or nervous exhaustion. Further inquiry will in many cases reveal a relationship between symptoms which apparently originate in the biliary tract and that large group of disorders of gastric, duodenal, and colonic physiology.<sup>8</sup> That the endocrine system is also indirectly involved in the production of these symptoms is suggested by their frequent onset during or following the menopause, as well as their being associated with disorders involving the thyroid gland.

*Pain:* The accuracy of the history and diagnostic tests is best shown by a study of the findings in patients coming to operation. In a series of 250 cases carefully reviewed, we have arrived at several conclusions of interest. The first is the fact that biliary colic, regardless of how typical the attack may be, does not necessarily mean stones. This knowledge deserves emphasis because frequently colic is considered proof of stones and therefore an indication for operation. Most recent evidence seems to indicate that colic results from the sudden overdistention of either the gall bladder or the common duct as the result of obstruction to the outflow of bile. The cause of the obstruction may be stones, spasm or organic disease (Morley,<sup>9</sup> Hurst,<sup>10</sup> Zollinger<sup>11</sup>).

Because pain proved to be the most prevalent symptom in the series studied, further observations of its characteristics seemed justified. While biliary tract pain is described as typically originating in the right upper quadrant, no less than half of these patients described the pain as being in the epigastrium. Hurst,<sup>10</sup> incidentally, has made similar observations. Radiation furthermore was in many cases atypical, being to the left side or precordium, especially with obstruction of the cystic or common ducts (Carter<sup>12</sup>). Among other symptoms of particular significance were nausea and vomiting, which occurred most commonly with overdistention of the common duct, as noted by Zollinger.<sup>13</sup> Chills and fever or jaundice were usually associated with both obstruction of the common duct and infectious cholangitis.

*The Cholecystogram:* The routine oral use of the double dose of dye has been attended by a notable increase in accuracy, particularly in the detection of stones (Stewart and Illick<sup>14</sup>). Technique has furthermore been improved by the use of paregoric to intensify the gall bladder shadow through its effect on the sphincter of Oddi, as well as to prevent loss of dye by diarrhea. The removal of excessive gas by enemas and the hypodermic injection of Prostigmine have also proved useful procedures.

In the interpretation of cholecystographic findings, a correlation with operative findings by Heyd, Carter and Hotz<sup>15</sup> has shown that the intensity of the gall bladder shadow is, in most cases, a reliable indicator of its concentrating ability, provided functional disturbances have been ruled out. In other words, faint visualization of the gall bladder which filled and emptied normally indicated active or past infection with fibrosis in 87 per cent of the patients coming to operation. Stones are difficult to visualize in these cases. However, a poor concentration of dye and consequently a faint visualization was found to occur with a gall bladder capable of normal concentration, when there was a disturbance of liver secretion or interference with the flow of bile into the gall bladder. On the other hand, a normal visualization of the gall bladder may occur in the presence of definite disease, particularly if there is impaired emptying. Further observations have shown that a lack of gall bladder shadow is not a reliable diagnostic sign unless the dye can be simultaneously visualized in the colon. This is assurance that the dye has been taken and has not been lost by vomiting or diarrhea. The most common operative finding in patients having had pain and showing no visualization of the gall bladder is a cholesterol stone impacted in the

cystic duct. Statistical studies have almost invariably shown that the stones found at operation can actually be demonstrated in the cholecystogram in only about 25 per cent of patients.

The cholecystogram, furthermore, affords usually unrecognized evidence of functional disorders in the enlarged gall bladder shadow, which is frequently of unusual intensity; confirmatory evidence is found in a delay in emptying of the gall bladder following a fatty meal. The general use of cholangiography (Mirizzi<sup>16</sup>), or visualization of the biliary tree by the injection of a radiopaque substance through the "T" tube during or following operation, should greatly reduce the incidence of postoperative colic due to retained common duct stones. Our conclusions in regard to the x-ray studies are that although these methods have attained a remarkable degree of accuracy, they must not be considered entirely infallible. They are simply a part of our diagnostic investigations; all other findings must also be taken into consideration in arriving at a final diagnosis.

*Biliary Tract Drainage:* Under the circumstances, it is indeed fortunate that there is available a dependable supplementary diagnostic method; that of biliary tract drainage (Lyon<sup>7</sup>). Numerous investigators have proved that the microscopic examination of the biliary sediment affords reliable evidence of infection or stones, just as similar evidence may be found in an examination of urinary sediment (Lyon<sup>7</sup>, Piersol and Bockus,<sup>17</sup> Reh fuss,<sup>1</sup> Rousselot<sup>18</sup>). Investigation of several hundred patients coming to operation, however, shows that crystalline sediment may indicate stasis rather than stones.

Furthermore, it is now possible to demonstrate with considerable accuracy actual infection of the biliary tract with the encapsulated duodenal tube.<sup>19</sup> In a series of 120 operative patients reported by Twiss, Carter and Hotz,<sup>20</sup> preoperative duodenal drainage showed all specimens of duodenal bile to be sterile in seventy-four of seventy-five cases where the biliary tract was proved to be sterile by specimens obtained at operation. Of twenty-eight cases showing positive duodenal cultures of significant organisms, twenty-five had identical types of organisms in the biliary tract at operation. The encapsulated tube and its use have been described by Twiss and Phillips.<sup>21</sup> These facts are of great practical importance because in all published reports the least satisfactory results of cholecystectomy have been obtained in those patients having neither stones nor infection.

Aside from its value in the demonstration of organic pathology, biliary tract and common duct drainage has furnished much of the evidence upon which the vast and growing volume of literature pertaining to functional disorders of the biliary tract is based. Its contributions here are mainly the demonstration of abnormalities in gastric acidity, which are found in the majority of patients with biliary tract disease, and the variations in the amount and concentration of bile obtained following stimulation. There is, moreover, no test of greater accuracy for complete obstruction of the common duct, a finding usually indicating malignancy, or for the absence of pancreatic ferments, which is sometimes found in pancreatic disease. A word of warning must here again be sounded, however, for no conclusion can be based upon the findings of a biliary tract drainage which has not been properly performed.

A discussion of diagnosis cannot of course be left without mentioning that there is a multitude of tests which have been devised for the purpose of demonstrating impairment in liver function or differentiating between the obstructive and intrahepatic types of jaundice. Each of these has its enthusiastic adherents, few, however, have come into general use or obtained unanimous approval. While many of these procedures have undoubtedly great value, a discussion of their relative merits would be far beyond the scope of the present paper.

*Differential Diagnosis:* Failure in treatment may indicate that the symptoms for which the patient is being treated did not originate in the biliary tract, or that the relationship between the biliary tract symptoms and other disorders was not sufficiently well understood. Among other disturbances which we consider to be due to an imbalance of the autonomic nervous system is spastic colitis, characterized usually by abdominal pain, constipation, mucus in the stool, a spastic colon and the finding of hyperactive reflexes.<sup>22</sup> Among other apparently related conditions are pylorospasm and duodenitis, which are usually characterized by some relationship of symptoms to the intake of food. Another condition is peptic ulcer, the diagnosis of which is suggested by pain occurring regularly before or after meals, or at the same time every night. Inflammatory lesions of the appendix and urinary tract quite commonly produce difficult diagnostic problems; the presence of a right-sided ureteral stricture or renal calculus may also be confusing. The finding of gall bladder dysfunction secondary to such conditions should not prevent attention

being focused primarily upon the original cause of the patient's symptoms. In any patient having precordial or epigastric pain, we must carefully determine whether the pain originates in the biliary tract or in the heart, remembering that both may be involved. Finally, the possibility of tabetic crises must never be forgotten.

### SOME PROBLEMS IN MANAGEMENT

In discussing the medical management of biliary tract disease, the question which immediately becomes apparent is, "What type of case do you include in this group?" The answer is that every patient with biliary tract disease is a candidate for a careful complete diagnostic investigation, followed by continued medical supervision, regardless of the necessity of surgical intervention. Both infections and functional disorders of the biliary tract are with few exceptions chronic and recurrent in character, as careful follow-up investigations have shown. The situation has been admirably summarized by Lahey and Jordan:<sup>23</sup> "The management of biliary tract disease, like the management of almost all other intraabdominal diseases, has become a joint problem of the surgeon and internist. While the treatment of gall bladder infection and stones and of cholangitis are admittedly surgical, the diagnosis and post-operative treatment of these conditions present problems of great interest to the internist."

The initial and immediate problem which confronts the physician in any given patient might be expressed by the questions:

"Is this a medical or surgical case?"

"What are the indications for treatment?"

Satisfactory answers to these questions are furnished by an adequate diagnostic work-up, which quite frequently necessitates more information than can be obtained by the usual history, physical examination, and cholecystogram. Not even direct positive evidence of the fundamental factor of infection can be obtained by these limited means. However, the necessary information may be obtained by other methods such as biliary tract drainage, chemical examination of the blood, and liver function tests.

The first step in diagnosis is a differentiation between organic disease and functional disorders of the biliary tract. Although control of the entire digestive tract by the autonomic nervous system has always been known, the mechanism of the biliary tract has only recently been suffi-

ciently understood to be of practical value. A study of functional disorders of the biliary tract was probably originated by Westphal,<sup>24</sup> the importance of whose concepts has been stressed in the American literature by Ivy and Sandblom,<sup>25</sup> under the term of biliary tract dyskinesia. The basic classification of these disorders is into atonic and hypertonic types of gall bladder enlargement.<sup>26,27</sup>

*Functional Disorders:* The atonic type of gall bladder enlargement is commonly found in patients showing a general debility, usually in those of middle age or advanced years who are addicted to sedentary habits and overeating. Their history is characterized by dull pain or discomfort, especially after meals, belching, distention, nausea, and constipation. The cholecystogram shows an enlarged balloon-shaped gall bladder with impaired power of evacuation, as demonstrated by lack of emptying following the fatty meal. On biliary tract drainage, there is usually a deficiency of free hydrochloric acid, with a large amount of concentrated bile which is obtained only after stimulation of the gall bladder with olive oil.

The hypertonic gall bladder associated with gastric hyperacidity often gives, in addition to the dyspepsia previously described, symptoms of colic and heartburn. On physical examination there may be tenderness in the right upper quadrant. This, however, seems to be due to overdistention of the gall bladder and disappears following duodenal drainage. The cholecystogram shows in these cases a tubular type of gall bladder enlargement with a dense shadow, commonly with a delay in emptying following the fatty meal. Biliary tract drainage findings include gastric hyperacidity; concentrated bile is obtained following stimulation. Cultures of duodenal bile are usually sterile.

The hypertonic gall bladder of the reflex type is similar in symptomatology to that described with gastric hyperacidity. Acute symptoms are more apt to follow an emotional disturbance or physical or nervous exhaustion. Here again there may be tenderness in the right upper quadrant, which disappears after duodenal drainage. The cholecystogram differs in showing, during periods of freedom from pain, prompt and almost complete emptying following the fatty meal. On biliary tract drainage concentrated gall bladder bile is easily obtained following stimulation with magnesium sulphate. Cultures of duodenal bile are again sterile. The essential feature of the hypertonic reflex gall bladder, however, is the presence of some source of reflex irritation which results in



a spasm of the common duct sphincter and a resultant overdistention of the gall bladder and common duct. The reflex cause may be in the central nervous system, induced by worry or fatigue, or it may lie in some pathological condition of the abdominal cavity, such as a chronic appendicitis, renal calculus or pyelitis. Carter and Hotz<sup>28</sup> recently reported three cases in which improved function of the gall bladder followed the removal of a diseased appendix.

In functional disturbances particularly of the hypertonic type there are, practically invariably, evidences of disturbed function of the autonomic nervous system, which controls the function of the entire biliary and digestive tracts. It is therefore of clinical significance to be able to ascertain the presence of an imbalance of the autonomic nervous system. While patients having this disorder may be the picture of composure, they are usually of the nervous, hyperactive, worrying type. Environmental disturbances which cause symptoms can frequently be found by a careful history. The most common physical findings are a postcervical tension and tenderness, dilated pupils, a spastic colon (with a palpable tender sigmoid and a dilated cecum), and generally hyperactive reflexes.

*Chronic Non-Calculous Cholecystitis:* Since this term is in use to designate cases of every possible degree of inflammation and infection,<sup>29</sup> as well as many in whom there is no infection whatsoever, it is first necessary to define our terms. Graham<sup>30</sup> and Mackey<sup>31</sup> have suggested the following classification: (1) Minimal lesion, wall of gall bladder slightly thickened, few lymphocytes in wall, concentrated bile in the gall bladder, (2) cholesterosis, (3) chronic catarrhal cholecystitis—edema of mucosa, greater lymphocytic infiltration, some muscular thickening, (4) chronic fibrous cholecystitis, markedly thickened walls, diverticular crypts, an absence of cuboidal epithelium, usually associated with calculi. Heyd, Carter and Hotz<sup>15</sup> offer a similar but somewhat more comprehensive classification, in which dysfunction is considered a preliminary step to stone formation and infection, as well as the various subsequent pathologic changes in the biliary tract. In non-calculous cholecystitis, an accurate initial classification is essential, because the effectiveness of cholecystectomy in the relief of symptoms is directly proportional to the amount of pathology present. A statistical study of operative cases and pathological specimens has shown in most instances that where symptoms have not been relieved by cholecystectomy there is little or no pathological change in the gall bladder wall.

The presence of chronic cholecystitis may be suspected with a history which includes pain of the character previously described, dyspepsia, an intolerance for fats, and constipation. Symptoms of more extensive pathological changes are nausea, vomiting, chills, fever, jaundice, and loss of weight. Tenderness and spasm of the right upper quadrant are to be found during active phases of the disease. As indicated by a study of those patients coming to operation, the cholecystogram will in most cases show impairment in the degree of visualization of the gall bladder; with no visualization there are generally stones. The biliary tract drainage usually shows pathologic elements in the biliary sediment, an impaired response to stimulation in obtaining concentrated gall bladder bile, and positive cultures in specimens of duodenal bile obtained under sterile precautions.<sup>32</sup> An additional finding, common during active stages of infection, is a moderate elevation of the icterus index reading,<sup>33</sup> even in the absence of jaundice.

Since differentiation between true cholecystitis and dyskinesia is highly important, the differential factors as demonstrated primarily by operative findings should warrant a brief discussion. The symptoms apparently most suggestive of cholecystitis are acute prolonged attacks of pain, chills, fever, loss of weight, and jaundice. Pain is usually associated with soreness or tenderness in the right upper quadrant. In cholecystographic studies, cholecystitis cases usually show faint or no visualization of the gall bladder. On the other hand, the cholecystogram in uncomplicated functional disorders shows a strong concentration of dye and a characteristic enlargement of the gall bladder with delayed emptying after the fatty meal. The fact must be constantly kept in mind, however, that in many patients both functional disorders and infection are present.

Having arrived at the diagnosis of chronic cholecystitis, it is next necessary to determine whether medical or surgical treatment is preferable. Surgery is usually necessary with a history of recurrent acute attacks of pain, nausea, vomiting, chills, fever, or jaundice. Patients with these symptoms rarely respond well to medical treatment. In a study of 3872 operative cases reported by Heyd, Carter and Hotz<sup>15</sup> these symptoms have been found to be associated most frequently with advanced pathology involving the common duct. The advisability of surgery is confirmed if the history described is associated with findings of acute tenderness, spasm, or a mass in the right upper quadrant; faint or no

visualization of the gall bladder; biliary drainage findings of an absence of normally concentrated gall bladder bile. Further evidence is furnished by the presence of pathologic microscopic elements and positive cultures of pathogenic organisms in the duodenal bile. With these findings there may be a moderate elevation in the icterus index reading. Medical treatment is indicated (in the absence of the recurrent acute symptoms previously mentioned) when the cholecystogram and biliary tract drainage indicate a fairly normally-concentrating gall bladder, with sterile or positive cultures of duodenal bile, and a relatively normal icterus index. Mentzer<sup>34</sup> however states, "all patients with chronic non-calculous cholecystitis are entitled to a trial period of medical treatment."

*Cholesterosis:* By cholesterosis of the gall bladder is meant the "strawberry gall bladder" described by Moynihan and MacCarty.<sup>35</sup> The title is derived from the appearance of the mucous membrane of the gall bladder, which is covered with tiny yellow plaques of cholesterol esters and fats. While the causes of this condition and the best methods of treatment have aroused a great deal of speculation, a very comprehensive study by Mackey<sup>31</sup> seems to indicate that the deposits in the wall of the gall bladder are simply the result of excessive absorption of cholesterol from a supersaturated solution of gall bladder bile. The conclusions of this author are that cholesterosis of the gall bladder is in itself not entitled to the designation of a clinical entity; that it cannot be diagnosed with assurance clinically; and that the symptoms and indications for treatment in this condition are entirely dependent upon the degree of concomitant cholecystitis.

*Cholelithiasis:* While in general cholelithiasis is conceded to be surgical, the problem of the patient with stones and without acute symptoms will always be with us. An excellent study of stone formation has been reported by Sweet.<sup>36</sup> In these cases the gall bladder may visualize and empty normally or there may be no visualization in the cholecystogram and no concentrated bile obtained on duodenal drainage. Additional findings may be positive bacteriological cultures of duodenal bile and a moderate elevation of the icterus index. In the latter group is usually found active infection<sup>37</sup> or a non-functioning gall bladder with a calculous obstruction of the cystic duct. There is at other times advanced pathology of the gall bladder, common duct and liver (Heyd, Carter and Hotz;<sup>15</sup> Heyd and Killian;<sup>38</sup> Graham<sup>30</sup>). Recurrent acute attacks and laboratory findings of infection, advanced pathology, or a non-

functioning gall bladder would seem to justify advising prompt surgical interference, since impairment in the blood supply in many cases results in gangrene or perforation of the gall bladder. In 167 cases of cholelithiasis, under observation but not operated upon for various reasons, 10 per cent developed acute cholecystitis.

*Acute Cholecystitis:* The first and foremost consideration, and this is a fact which is frequently overlooked, is that acute cholecystitis is in approximately 90 per cent of the cases an acute exacerbation of a chronic cholecystitis, with cholelithiasis. Therefore, advanced pathology may be suspected in the patient with acute symptoms, especially if there is a prolonged history of indigestion and presence of acute tenderness and a mass in the right upper quadrant. Especially in the aged, the absence of fever and leukocytosis is by no means uncommon, even in the most advanced stages of pathology. The sedimentation rate may serve as a more reliable indication of the severity of the infection, or of the presence of empyema or gangrene of the gall bladder.

These facts have a very definite bearing on the spirited and prolonged controversy over the relative merits of the "immediate" and "delayed" operation in acute cholecystitis. Statistical studies have proven both sides to have been at least partially right in their contentions. Heuer states that gangrene and perforation occur in at least 20 per cent of all cases of acute cholecystitis not operated upon promptly. Hotz<sup>39</sup> in a study of 574 cases of acute cholecystitis, states that gangrene was found at operation in 17 per cent of the cases and perforation in 16 per cent. The general mortality in this series was 10 per cent; in acute perforated cholecystitis the mortality was 26 per cent. With peritonitis, which occurred in 77 per cent of patients with perforation, the mortality was 39 per cent. Hotz<sup>40</sup> concludes that "perforation of the gall bladder during an acute attack is as frequent and as fatal from a statistical review as that in acute appendicitis."

In regard to the optimum time for operation in acute cholecystitis, the picture has been in the past confused by statistical studies based upon the time of operation after the patient has entered the hospital. By a study of the elapsed time from the onset of acute symptoms, Hotz<sup>39</sup> found that the mortality showed a great variation, which depended upon the day of illness upon which the operation was done. From the first to the fourth day there was a progressive decrease in mortality from 12 per cent to 4 per cent; after the fourth day there was a progressive rise. The

conclusions based upon these studies were that prompt operation in most cases of acute cholecystitis is preferable, provided a period of at least 24 hours is allowed in the hospital to prepare the patient for operation. The essential features of preparation consist in relieving dehydration and building up the glycogen reserve of the liver, by giving dextrose by mouth and infusions if necessary.

### THERAPEUTIC CONSIDERATIONS

The principles of treatment here outlined have been formulated and followed during the past ten years in the Biliary Tract Clinic of the New York Post-Graduate Hospital. A detailed diagnostic investigation has been completed in 2,100 patients; conclusions as to the results of treatment are based upon approximately 20,000 clinic visits. The diagnostic routine has included the cholecystogram, biliary tract drainage, and chemical analysis of the blood. Practically all patients suspected of having infection or coming to operation have had cultures made of bile; for several years this has been obtained by means of the encapsulated duodenal tube.

*Preoperative Care:* Surgical patients are admitted when possible several days before operation. During this period the patient is given a high caloric, high carbohydrate diet, low in proteins and fats. Lumps of sugar, dextrose or candy are given every two hours; water or fruit juices every hour or two. When necessary, dehydration is relieved by clyses or intravenous infusions of 5 per cent glucose, care being taken not to overload the circulation. With jaundice, which involves the possibility of hemorrhage and results in a greatly increased mortality, the preoperative administration of bile salts and vitamin K is indicated for at least 4 days preceding operation. The amounts are judged by the results of the prothrombin time (Snell, Butt and Osterberg<sup>41</sup>).

*Postoperative Care:* In several hundred patients reporting for relief of digestive symptoms following cholecystectomy, practically none was following any dietary restriction. Most patients had been told that they were "cured" and could "eat anything." In our experience, recurrent symptoms are less common with a diet restricted in the intake of fats and foods high in cholesterol,<sup>42</sup> as well as those foods which are indigestible and high in roughage. We also feel that the general hygienic care of the patient merits continued supervision, especially in regard to the intake of an adequate amount of fluids, sufficient exercise, and the avoidance of

overeating and constipation. Medication in these patients is seldom needed and is given only in accordance with specific indications furnished by the history, physical examination, or laboratory findings.

*Medical Regime:* The general principles of treatment in medical patients are based upon the initial diagnosis and the results of diagnostic tests, as well as upon the personality of the patient and his environment. An effort is made to direct treatment to physiological needs, whenever this is possible. In functional disorders, rest or a complete change of environment is frequently beneficial, as is the removal or treatment of any pathological conditions of the abdominal cavity. General hygienic care is of the utmost importance in all ambulatory patients, especially in those having infections. Removal or treatment of focal infections should also receive consideration. The more serious conditions, particularly those associated with jaundice and fever, should have bed rest.

*Diet:* The opinion of Chauffard and Rehfuess and Nelson<sup>1</sup> has been confirmed by our experience, in that there is no more important element than diet in the treatment of disorders of the gall bladder or liver. Diets formulated in our clinic for gall bladder disease are of three types:<sup>13</sup> (1) Low fat and low cholesterol, (2) Modified Sippy, (3) "Stimulating," or relatively high cholesterol and fat. The diets and the indications for their use have been described in detail by Carter, Greene and Twiss.<sup>12</sup>

The low cholesterol and low fat types of diet have been in use for many years. The foods highest in cholesterol are egg yolk, brain, liver, kidneys, and sweetbreads. Both fats and cholesterol cause contraction of the gall bladder and when taken in excessive amounts tend toward a hypercholesteremia. The indications for the use of these diets are hypercholesteremia, cholelithiasis, a history of intolerance for fats, and any condition which interferes with the contraction of the gall bladder, such as inflammation or obstruction of the cystic or common bile ducts. The use of a low cholesterol and low fat diet results in a lowered blood cholesterol in most cases. Since weight variations in gall bladder disease are frequently extreme, this group of diets consists of the No. 1 diet, which is low in calories, and the No. 2 diet, which is high in caloric value, chiefly through intermediate feedings and the addition of foods high in carbohydrates.

The modified Sippy diets with intermediate feedings are intended for the patients with gall bladder disorders with gastric hyperacidity and the so-called hypertonic, hyperacidity type of gall bladder enlargement.

Clinically about 25 per cent of chronic disorders were found to fall in this group. This type of diet is also indicated in duodenitis, pylorospasm and in extreme degrees of spastic colitis. The 3 A diet is a strict carbohydrate diet with intermediate feedings, the 3 B diet a maintenance diet with the addition of meat.

By "stimulating" types of diet is meant those designed to relieve biliary stasis and to promote evacuation of the flaccid or atonic type of gall bladder. The contraindications to their use are fat intolerance, hypercholesteremia, cholelithiasis, active infection of the gall bladder and obstruction of the cystic or common ducts. Our diet No. 4 is low in caloric value; diet No. 5 is high in caloric value.

Another very important member of the dietary group is diet No. 6, which is high in carbohydrates and calories, low in proteins and fats. This diet is used in jaundice of all types, acute liver damage, and cirrhosis of the liver. The great value of this type of diet in relieving the ascites of cirrhosis has been demonstrated by the staff of the Mayo Clinic. It is also useful in building up the glycogen reserve of the liver before operation, and in increasing the weight of the patient who is suffering from malnutrition or recent weight loss.

*Medication:* Aside from the dietary and hygienic measures discussed, efforts are made to give medicines only in accordance with definite indications. Among the relatively few which we have been using are the following:

*Laxatives:* Constipation is one of the most common symptoms associated with biliary tract disease. As a result, the liver probably frequently suffers from impaired function due to actual infection or toxic absorption as suggested by Rehfuß<sup>1</sup> and by Bassler.<sup>44</sup> Where possible, an adequate amount of exercise and fluids are advised. Saline laxatives have a definite place; among those most effective are Epsom salts, Carlsbad salts, sodium phosphate, sodium sulphate and many similar preparations. In spastic hypertonic conditions, lubricants are preferable, such as mineral oil, agar, Irish moss, and combinations of these medicines. Bile salts and their combinations with various types of cathartics should be limited to patients who do not have spastic colons or biliary dyskinesia. Cathartics in general are contraindicated except in the aged, in whom vitamin B is especially useful.

*Alkalies:* The prevalence of gastric hyperacidity with disorders of the gall bladder is rarely suspected, because the gastric acidity of these

patients is hardly ever tested. However, in many with colic, heartburn and indigestion almost immediate relief can be obtained by the modified Sippy diet and alkalies following meals. These medicines give best results when taken an hour after eating. Among medicines which have proved satisfactory are equal parts of calcined magnesia and calcium carbonate, to which an equal part of bismuth subcarbonate may be added if desired. By adjusting the amount of laxative element, which is calcined magnesia, this powder may be made as laxative as desired. The aluminum hydroxide preparations have also seemed to give good results in one to two dram doses, their greatest disadvantage is the tendency toward constipation which sometimes follows their use. The newer magnesium trisilicate preparations, Trisomin and Trinesium, have also given very satisfactory results. Their greatest advantage is the convenience of tablet medication.

*Hydrochloric Acid:* In patients having an achlorhydria as demonstrated by the Ewald meal, remarkable relief may sometimes be obtained by taking a dram of dilute hydrochloric acid in orange juice with meals. Nitrohydrochloric acid, 10 minims in water, has also been advocated in these conditions. When acids are not well tolerated, one or two capsules of Acidulin may be given with meals.

*Cholagogues and Cholaretics:* Cholagogues are substances which cause contraction of the gall bladder, primarily fats, cholesterol-containing foods and oleic acid. Cholaretics are substances which will stimulate the liver to secrete more bile. The only preparations demonstrated as being of practical value in this regard are the bile salts. While there is no question about the efficacy of bile salts in stimulating bile flow, there is some question as to their therapeutic indications. Duodenal drainage studies have conclusively shown that the liver secretes with remarkable consistency a definite amount of bile salts daily. In approximately 1200 c.c. of bile secreted daily, possibly 10 grams of bile salts are discharged into the intestinal tract. A large part of this is reabsorbed and carried back to the liver, where it exerts a cholaretic action. There is, therefore, probably an adequate amount of bile salts delivered by the liver under all circumstances except where there is a complete obstruction of the common duct or where liver damage has resulted in an almost complete loss of function. There is a real question whether bile salts should be administered at all under these conditions.

While bile salts are apparently beneficial in the atonic gall bladder



and in the aged suffering from constipation, contraindications to their use would seem to be hypertonic states of the biliary or intestinal tracts, duodenitis and pylorospasm. Under these conditions an increased intra-hepatic pressure has been found to aggravate the discomfort of the patient, especially if antispasmodics are not given simultaneously.

*Antispasmodics:* With pain, colic and in the hypertonic conditions of the biliary tract, as well as in the spastic colon, the antispasmodics play a very beneficial role. Among those found very effective are atropine sulphate, extract of belladonna, tincture of belladonna, Trasentin, Syntropan and Bellergal. The three latter preparations have seemed less apt to produce dilatation of the pupils and a dry throat than the atropine preparations. Adequate doses, however, are essential to produce results in this group.

*Sedatives:* The highly nervous state of a large number of these patients justifies a sympathetic consideration of the individual case and the use of sedatives in as large doses as needed. The relation of nervousness and worry to symptoms has previously been discussed. The findings of a postcervical congestion, a spastic colon, and hypertonic reflexes suggest the need of sedatives. Among those which we have used with satisfactory results are phenobarbital, grains  $\frac{1}{4}$  to  $\frac{1}{2}$ ; Adalin, grains 5; triple bromides, 15 grains, three times daily. Bromural and Bellergal have also been given, 1 tablet three or four times daily.

*Biliary Tract Antiseptics:* Although many drugs have been advocated as biliary tract antiseptics, few actually have proven to be effective in this regard. Since the only method aside from operation by which infection in the biliary tract can be actually demonstrated is by the bacterial cultures of the duodenal bile obtained under sterile precautions, the organisms must be demonstrated as being present before treatment is begun and persistently absent after treatment has been stopped. We know of no such demonstration with any drug.

On the other hand, the known excretion in the bile of certain drugs, such as neoprontosil and sulfanilamide, affords possibilities for further study. Good clinical results in the treatment of liver infection with sulfanilamide have been reported by Ottenberg.<sup>45</sup> Since investigations have shown that this drug is secreted in good concentration in the bile, encouragement is provided for the further study of this type of treatment.

*Vaccines:* The use of autogenous vaccine from the bile, stool or from foci of infection has been advocated and in use for many years by

Rehfuss.<sup>1</sup> We have also utilized vaccine for the past ten years and have been very well satisfied with its results in many cases. Best results are obtained if the dosage is kept very low, below the point of systemic reaction. The course of treatment, however, should be continued for at least four to six months. While there may well be some question as to the exact mechanism by which the benefit is obtained, good results are frequent in patients having this form of treatment.

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AGING OF THE CARDIOVASCULAR SYSTEM\*

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AGING is a biological phenomenon which has been the subject of much study, but the processes that underlie the aging of tissues and organisms are not yet understood. When we try to apply general biological knowledge of the aging mechanism to clinical medicine and to an understanding of senescence in man we at once encounter the problem: What is aging, what disease? What organic bodily changes are a result of the inevitable involution of tissues and organs, what a result of environmental and accidental factors? Our answer to these questions will determine the direction of scientific study of senescence, as well as the therapeutic approach to persons suffering from the so-called degenerative diseases which are commonly regarded as phenomena of aging.

The distinction between aging and diseases is not an academic one; it is not just a juggling with words. To quote a famous philosopher and teacher: "If names be not correct, then language is not in accordance with the truth of things. If language be not in accord with the truth of things, affairs cannot be carried on successfully."<sup>1</sup>

What do we mean by aging? Aging is one phase of the life curve.

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We are accustomed to think of youth as the period of growth, of aging as the period of decay or involution. But as Huxley<sup>2</sup> has stated: "Development and Life are, strictly speaking, one thing; though we are accustomed to limit the former to the progressive half of life, and to speak of the retrogressive half as decay, considering an imaginary resting point between the two as the adult or perfect state."

Ehrenberg<sup>3</sup> has stated the law of the necessity of death. Death is necessary for life; without death there is no life. All life is a running down that of necessity leads to an end. There is no such thing as a stationary life. Every person has his own physiological time of death, even if he does not live to experience it. His true age is determined, not by the number of years he has lived, but by the number of years by which he is removed from death.

Minot<sup>4</sup> points out that "The period of old age, so far from being the chief period of decline, is in reality essentially the period in which the actual decline going on in each of us will be the least. Old age is the period of slowest decline."

Death may result from wear and tear of the organism due to external insults; it may result from the accumulation of inhibiting substances within the organism; it may result from a diminution in the original vital force. As Warthin<sup>5</sup> maintains, old age may be due to the gradually weakening energy charge set in action at the moment of fertilization of the egg. It has been said that the tempo of aging is dependent less on the degree of wear and tear, than on the inborn strength of resistance to this wear and tear. Senescence is but one phase of the continuous development, growth and differentiation of the living organism between the events of fertilization of the egg and death.

The variability of the time of occurrence of the individual phenomena of growth and senescence increases greatly with the progress of years. Thus the variability of the age at which the fontanelle closes, or at which the first teeth erupt is much less than that of the development of presbyopia. So it may be expected that physical disablement due to aging will appear at widely scattered ages, say at age 50 in some, at age 80 in others. This leads to further confusion and to difficulty in determining what phenomena are due to disease, and what to aging. At times the familial behavior of these phenomena may be helpful in reaching a decision, for the tempo of aging and of growth is often a familial characteristic. We often find members of one family growing

gray at about the same age, an age characteristic for each family.

Yet all structural changes found in the aged are not signs of senescence. The older the person, the greater his years of exposure to external insults, and the greater the possibility that his body will show scars of these encounters. A generation ago, when tuberculosis was far more widespread than it is today, almost every adult, at autopsy, gave evidence by the scarring of his lungs that he had undergone a tuberculous infection. These scars were not manifestations of aging; but aged individuals, because of years of exposure to tuberculous infection, almost universally had at some time been infected.

We shall all agree that there is an aging process of the various tissues and organs of the body. We may not agree where to draw the line between phenomena of pure senescence and those of superimposed disease, a disease process whose development, mayhap is favored by the aging of the tissues. Fractures of the hip, through the neck of the femur, are very common in old persons. Yet we do not regard such fractures as manifestations of aging. Aging plays its part; the bone has become rarified and brittle; the aged person has lost some of his resiliency, balance and coördination, so that he falls more easily and the weakened bone breaks more readily. But the actual fracture is an accident; it does not connote aging. Similar considerations apply to the so-called hypostatic pneumonias of the aged. Loss of elasticity of the lungs, rigidity of the thoracic cage, diminished excursion of the diaphragm, all presumably favor the collection of secretion in the lungs and prevent the expulsion of this material when it becomes infected. The element of infection, however, is an accident, not a manifestation of aging.

It has repeatedly been pointed out that natural death, death from natural decay, occurs very rarely in man.<sup>6</sup> Autopsies on old people always reveal a pathological cause of death, though no symptoms were observable during life. Thus Aschoff<sup>7</sup> reports on 400 autopsies on persons over 65 years of age. The most common causes of death were arteriosclerosis of the coronary, cerebral or peripheral arteries, hypertension, carcinoma of the gastrointestinal tract, prostatic hypertrophy, tuberculosis, and street accidents.

Can arteriosclerosis, and the resulting clinical phenomena be explained on the basis of aging alone? Arteries do change with the years, and certain basic elements of this change may be due to the inevitable senes-



cence of living tissues. But does this mean that coronary artery sclerosis in a man in his fifth decade, in a man who exhibits no other manifestations of bodily decay, is evidence of early senescent change? How reconcile this with a report such as that of Humphry<sup>8</sup> who examined 824 persons between the ages of 80 and 100 and found an absence of evident arterial disease in 72 per cent; or an autopsy performed by Professor Cunningham on a man aged 106 whose arteries throughout the body were slightly dilated, but with no decided signs of atheroma, and little loss of elasticity; whose heart was small and with healthy valves.

Groddeck<sup>9</sup> reports that in one-third of the autopsies of persons over the age of 80 there were only minimal arteriosclerotic lesions. If we insist that arteriosclerosis will develop inevitably in every person, that arteriosclerosis is a measure of the aging process, that early arteriosclerosis is evidence of early aging, must we not regard the absence of arterial disease in the aged as a sign that such persons are supernormal, that in them longevity, so far as it depends on an intact cardiovascular system, is a disease?

A striking example of the difficulty in distinguishing between aging and disease is described by Crocker<sup>10</sup>. Many plants which reproduce vegetatively degenerate and become senescent in due time, and to obtain new vigorous specimens it is necessary to reproduce them from seed from time to time. For years it was supposed that this was a true senescence due to the absence of the rejuvenating power of the sexual conjugation. More recently it has been learned that these plants degenerate because of the accumulation of virus diseases in them, and that since virus diseases are rarely transmitted through seeds, sexual reproduction leads to rejuvenated healthy stock. Virus-degeneration was mistaken for age-degeneration.

It is instructive to note that the human changes most characteristic of aging, bodily changes that are accepted, in the popular mind too, as evidence of senescence are: loss in height, loss in weight, presbyopia, deafness for high tones, graying of the hair, loss of elasticity of the skin. None of these alterations of the structure and texture of the body are regarded as disease processes, none of them challenge the continuance of life.

Can we find similar changes in the circulatory organs that seem to signify aging, and not disease? A characteristic phenomenon of aging of the heart is brown pigmentation of the muscle fibers. This pigment

accumulation first appears at the end of the first decade of life, and progressively increases. It is found in hypertrophied, as well as in atrophied heart muscle cells. The absolute weight of the heart diminishes with age, but the ratio of the heart weight to body weight shows some increase. Simple atrophy begins at about age 70, and is followed by a degenerative atrophy of the heart muscle fibers. This cannot be distinguished from the atrophy due to inanition and cachexia, and is probably due to a reduction in metabolism. The specific conduction system of the heart does not share in this atrophy and therefore becomes relatively more prominent. The sinuses of Valsalva become deeper; the mitral valve becomes too large, so that it bulges upward like an umbrella. These changes are distinct from calcification of the annulus fibrosus, and from atherosclerosis of the valves.<sup>7,11</sup> With age there is an increase of the elastic tissue in the heart, especially in the auricles.<sup>12</sup> Different parts of the heart undergo different changes with age. With advancing years there is a progressive enlargement of both auricles and of the four valvular ostia of the heart. The portion of the left ventricle at the apex atrophies so that the infrapapillary space becomes smaller. Thus, as it grows older the heart changes in shape; the base becomes wider; the apex, more pointed.<sup>13</sup>

Aging of the blood vessels, both arteries and veins, manifests itself by dilatation and elongation due to progressive deterioration of the elastic tissue in the vessel wall. The arterial wall gives way both in a circular and longitudinal direction, and a tortuosity of the vessel results.<sup>14</sup>

A characteristic histologic change is the accumulation of finely divided calcareous material in the media.<sup>15</sup> Many arteries show a progressive thickening of the intima beginning during the first decade, which may become quite extreme with advancing years. The intensity of this process varies in different arteries and is far more marked in the anterior descending limb of the left coronary artery than in any others. Sappington<sup>16</sup> reports that the thickest radial artery at 65 years has no more change than a coronary artery at the age 20. It is not clear whether these intimal changes are physiological or pathological. Intimal thickening from splitting and increase of elastic tissue is evidently a physiological process, for it begins within the first years of life and occurs regularly in all but the smallest muscular arteries. Thickening of the intima after the fourth decade is due to increase of collagenous tissue and shows fatty, hyaline and calcific change as well. It is common, but

by no means universal in old age.<sup>17</sup> It would seem that, if old age alone were responsible for such arterial changes, they would be more uniformly distributed throughout the body.

Changes in function of the heart and arteries occur with advancing years. The pulse rate diminishes in frequency up to age 21 and then remains fairly constant until about age 65, when it tends to increase to a slight degree.<sup>18</sup>

Many studies have been made of the velocity of the pulse wave in man in relation to age. The velocity of the pulse wave, when measured with due regard to a number of variables, is a measure of the degree of arterial rigidity or loss of elasticity.<sup>19</sup> There is a progressive increase in the velocities of the aortic and radial pulse waves from about 4 meters a second in childhood to about 10 meters a second at age 65.<sup>20</sup> This is an expression of the progressive loss in elasticity of the arteries.

This arterial change leads to changes in the blood pressure. The idea that with increasing age there is a progressive rise in blood pressure still finds general acceptance. The term hypertension is employed far too loosely. True arterial hypertension, which so commonly leads to cardiovascular disease, is characterized by an elevation of both systolic and diastolic blood pressures. Systolic hypertension, without rise in diastolic pressure, has an altogether different mechanism, and is the result, not the cause of cardiovascular disturbances. It is encountered in persons with aortic insufficiency, and with hyperthyroidism. Here it is due to alterations in cardiac output.

The hypertension met with in the aged is also a systolic hypertension. Characteristically, in the later decades of life, the systolic blood pressure rises to about 140 or 160, while the diastolic pressure remains unaltered.<sup>21</sup> This systolic hypertension and increase in pulse pressure is not caused by a narrowing of the peripheral arterial bed, and does not place an added strain on the heart and arteries; it is the result of the loss in elasticity and the increase in rigidity of the aorta and large arteries, that find expression in the increased velocity of the pulse wave.<sup>22</sup> The increasing length and width of the aorta and large arteries compensates for their loss in elasticity and helps to keep the internal tension of the aortic wall constant.<sup>23</sup> Viewed from this aspect the increase in systolic pressure in the aged is an expression of loss in arterial elasticity, and in its effect on cardiovascular dynamics is a beneficent reaction. It is a mistake to parallel the high blood pressure states of every day

clinical experience with the blood pressure changes that accompany aging.

The electrocardiogram in the aged has no characteristics that distinguish it from that of younger persons. Studies by Levitt<sup>24</sup> and by Warnecke<sup>25</sup> both show that about one-quarter of persons over the age of 70, who are presumably normal, have electrocardiograms indicative of myocardial disease. Duthoit<sup>26</sup> found a greater number of abnormalities, but his material is not presented in a way that makes close analysis possible. These abnormal electrocardiograms are signs of disease, not of aging. More characteristic of aging, as such, is an increasing tendency to left axis deviation, an increase in the relative duration of systole, and a lessened frequency of sinus irregularity.<sup>27</sup>

The cardiac output per square meter of body surface, measured under basal conditions, declines very slightly in old age.<sup>28</sup> This decline results largely from the lessened oxygen consumption of the body.

We have learned that the several functions of the cardiovascular system that we are able to measure, the pulse rate, the blood pressure, the cardiac output, undergo relatively slight changes with advancing years. But this does not mean that the aged have a circulatory system as competent as it was in their youth. The aged make less demand on their hearts; they eat less; they avoid extremes of cold and heat; their physical activity is greatly lessened; they are unaware that their hearts have become weaker; they have little need for the great cardiac reserves that they had in their youth. When outward circumstances compel them to take the buffetings of life, as they did when they were younger, they discover that they lack adaptability, they cannot respond to the stresses of a physically active life. The behavior of body temperature in the aged illustrates this lack of adaptability. The body temperature of the aged is the same as that of the young, but the aged cannot stand the cold; in the winter time they must wear more clothes than they formerly did, they must live in warmer rooms, they like to huddle about stoves and radiators. As Cannon<sup>29</sup> has said, their homeostatic mechanisms, when subjected to stress have limited ability to preserve uniformity of the internal environment.

Let us return to the problem of arteriosclerosis. Can we find additional evidence that arteriosclerosis is a disease, and not a degenerative process of senescence? If arteriosclerosis is a phenomenon of senescence, it should be encountered with some degree of uniformity in arteries

throughout the body, it should appear with some degree of regularity, and with similar frequencies among persons of different races, and in the two sexes. Experience shows that this is not the fact. Arteriosclerosis, and particularly coronary sclerosis, is far less common among negroes than among whites.<sup>30,31</sup>

That arteriosclerosis is less common in women than in men is known to all clinicians and pathologists. We have already pointed out that arteriosclerosis is by no means universally present in the aged. In old persons who have died after having had aortic stenosis of many years duration the aorta is characteristically smooth and elastic, as though the valvular lesion had protected the aorta from the constant and persistent strain of the systolic ejection of the blood by the left ventricle. In coarctation of the aorta, there is marked sclerosis of the aorta proximal to the lesion, and little or no sclerosis distal to the stenosis.<sup>32</sup> Sclerosis of the pulmonary arteries is far less common than sclerosis of the systemic arteries, and when it is well developed there is almost invariably some process, such as mitral stenosis or extensive pulmonary disease, that has led to increased pressure in the pulmonary circulation.<sup>32</sup> In children wide-spread advanced arteriosclerosis is encountered in the presence of severe nephrosis.

Finally we may recall the peculiar frequency of arteriosclerosis in diabetics. In diabetics the percentage mortality from arteriosclerosis is one-third greater than for the population as a whole.<sup>33</sup> In persons who have had diabetes for 10 years or more, coronary artery disease as a cause of death is four times as frequent as in non-diabetics.<sup>34</sup> This arterial change in diabetics begins in early life. Hallock<sup>35</sup> has shown, by measurements of pulse-wave velocity, that arterial hardening appears early in young diabetics.

Hypertension, too, greatly favors the development of arteriosclerosis. It is much more common, and far more extensive in persons with hypertension than in those with normal blood pressures. Coronary arteriosclerosis is uncommon in women, but in women with hypertension it is frequently encountered, and in women with diabetes it is nearly as common as in men.<sup>36</sup>

All of these observations seem to point clearly to the fact that arteriosclerosis is not a simple wearing out of the arterial coats that comes with age, but that it is a disease, a disease, it is true, that manifests itself mainly, but by no means exclusively, during the period of senescence.

I do not believe that any thesis that attempts to explain the distribution of arteriosclerosis on the basis of aging alone and that would explain its occurrence in the younger decades by predicating a great variability in the age of onset of senescence will meet the facts. Leary<sup>37</sup> has stated that: "Atherosclerosis is a disease and not the inevitable consequence of age, since it appears in the young and may be highly selective in its localization."

The changes in structure and function of the heart and arteries that come with age are few and simple, and do not give rise to clinical syndromes of disease, nor do they lead directly to death. The important senescent changes are: pigmentation of the heart muscle fibers, atrophy of the heart muscle, enlargement of the valvular ostia and stretching and loss of elasticity of the valves. The arteries become elongated and dilated from the progressive deterioration of their elastic tissue, and there is some thickening of the intima. Under basal conditions the functioning of the heart and arteries suffices to meet the needs of the body, but the circulatory system, like the rest of the aging organism, has lost its resiliency, and the quick power of adaptation to changing external stimuli, so that the homeostatic function of the circulatory system becomes progressively impaired. The cardiac pump itself usually functions without faltering into advanced old age. Clinicians have often remarked that the hearts of the aged have exceptional strength in spite of the presence of heart disease.<sup>38</sup>

Arteriosclerosis is a disease of middle and advanced life. Recognition of this fact has very practical implications. Doctor Alfred Cohn has said: "If arteriosclerosis is an inexorable natural process, its prevention is impossible, and its treatment useless." We have tried to show that arteriosclerosis is not primarily a process of senescence. This must lead us to regard the so-called degenerative circulatory disorders of middle and advanced life not as manifestations of an inevitable wearing out of the body mechanism, but as disease states. They remain a challenge to scientific investigation, and a problem for constructive therapy.

Our concepts of the nature of these "degenerative disorders" will further determine the direction of public policy in the care of persons disabled by these conditions. If we regard these disorders as unavoidable expressions of senescence, we shall provide only asylums or refuges where these disabled aging persons, these worn out human derelicts, may live out the remainder of their declining years. When we have learned

to regard these circulatory disorders as the result of disease, we shall provide complete medical care for those who are ill, and encourage further study of the causes of these disorders that have become one of the major health problems of today.

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## HISTAMINE IN ANAPHYLAXIS AND ALLERGY\*

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THE application of immunological concepts to the study of the idiosyncrasies has formed the foundation for a sound scientific approach to these baffling conditions. The discovery of anaphylaxis and the assumption that idiosyncratic diseases are anaphylactic conditions, have been of great importance. The conception that allergic diseases (as they are called today) are "anaphylactic" diseases, in other words that allergy is "human anaphylaxis," has led to a heated controversy of long standing. The one school of thought contends that clinical allergy and experimental anaphylaxis, although resembling one another in certain respects, are fundamentally different conditions; the other school, to which I belong, believes with Hans Zinsser<sup>1</sup> that allergy in man "is based on an immunological mechanism basically identical with anaphylaxis in animals, superficially modified by human anatomical and physiological conditions."

Notwithstanding these theoretical differences of opinion, the practical approach to the therapy of allergic diseases elaborated on the basis of these immunological concepts is to combat them by specific desensitization with the causative allergen or allergens. This immunological approach has been very successful, and one can be well satisfied with the results when one compares the relative helplessness of former days with our present therapeutic achievements. More and more allergens have been discovered; more and more allergenic extracts are being used in the treatment of allergic diseases.

However, there are some of us who have become perturbed by this ever expanding multiplicity of allergens and who have striven towards reducing the treatment of allergic diseases to a common denominator; that is, we have aimed at non-specific treatment as opposed to specific desensitization. Many attempts have been made to this end; some of

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them were comparatively successful; few of them, however, could compare with specific desensitization in practical achievement; only one of them compares in theoretical soundness. It is this latter attempt and especially its theoretical foundation that I should like to discuss this evening.

Anaphylaxis and the recognition of its importance as a biological principle were first described in 1902 by Richet.<sup>2</sup> It was shown that re-injection of an antigen into an animal, after the lapse of an incubation period, led to dramatic symptoms, which were termed anaphylactic shock. During the following years various theories were advanced to explain the symptomatology of anaphylactic shock. However, none of them was really satisfactory. Not even the anaphylatoxin-theory, one of the most generally accepted ones, was able to explain satisfactorily the phenomena of anaphylactic shock.

In a paper on the physiological action of histamine, Dale and Laidlaw<sup>3</sup> stated in 1910: "We content ourselves with recording as a point of interest and possible significance, the fact that the immediate symptoms with which an animal responds to an injection of a normally inert protein, to which it has been sensitized, are to a large extent those of poisoning by beta-iminazolyl-ethylamine."

This was one of those bold conceptions of a genius which, conceived at a time when there were hardly any tangible facts on which to base them, prove to have been correct after years of painstaking labor. Later experiments on anaphylaxis led Dale<sup>4</sup> to the conclusion that "the symptoms of the anaphylactic reaction" are due, "not to the formation of a poison in the blood but to the reaction between the antigen and a precipitating antibody located in the cell protoplasm."<sup>5</sup> He further called attention to the close similarity between the anaphylactic responses of different tissues in various species of animals and the responses of those particular tissues to histamine; the symptoms of anaphylactic shock in the various species are the symptoms of histamine shock in each species. In different species these symptoms are determined by the reactions of different organs which have been termed "shock organs." Thus the shock organ in the dog is the liver, in the guinea pig the lungs.

There is, furthermore, considerable though not complete parallelism between the histamine sensitivity of a species and its anaphylactic response.<sup>6</sup> On the one hand the guinea pig, which is highly sensitive to histamine, is eminently susceptible to anaphylactic shock; on the other

hand the rat, which is highly resistant to histamine, cannot be made anaphylactic under normal circumstances.<sup>7</sup>

Histamine is the amine produced by decarboxylation of the amino-acid histidine. Its principal physiological actions affect the circulation, the plain musculature and the secretory glands.<sup>8</sup> Its circulatory actions are a constrictor effect on the arterioles and a dilator effect on the capillaries. This dilatation so increases the permeability of the capillary wall that fluid passes out from the blood stream into the tissues. Its action on plain musculature leads to contraction of various organs such as the uterus and the gallbladder, and to intense constriction in others, as in the lungs. Its action on the secretory glands consists of stimulation of their activity.

Histamine was prepared synthetically in 1907 by Windaus and Vogt.<sup>9</sup> In 1910 Ackermann<sup>10</sup> obtained it by submitting histidine to the action of putrefactive bacteria, and in the same year Barger and Dale<sup>11</sup> discovered the presence of histamine in ergot. But there was no proof that histamine occurred in animal tissues and it was hard to understand how it could be formed almost instantaneously in the course of the anaphylactic reaction. In the following years several attempts were made to isolate histamine from animal tissues,<sup>12</sup> but it was not until 1927 that Best, Dale, Dudley and Thorpe<sup>13</sup> were able to show conclusively that this base was a normal constituent of the liver and lungs. Later, many other tissues were also shown to contain histamine.<sup>14</sup>

In 1929 Dale<sup>15</sup> formulated his theory of anaphylaxis in the following words: "We may picture anaphylactic shock as the result of cell injury, due to the intracellular reaction of the antigen with an aggregating antibody. Whether this is general or localized in a particular organ, histamine will be released, and its effect will be prominent in the resulting reaction, imposing a general resemblance to the syndrome produced by histamine itself, on the symptoms seen in each species."

Up to this time there existed very little experimental evidence in support of Dale's theory, and the findings of Best and his co-workers naturally were of great importance. In the years preceding their discovery, other valuable contributions to the histamine theory had been made by Lewis and his associates. Lewis, who had described the so-called "triple response" of the human skin,<sup>16</sup> together with Grant compared the reaction of histamine and of fish extract in a fish-sensitive patient. Lewis and Grant<sup>17</sup> found that when histamine and a fish extract were

punctured simultaneously into this patient's skin, the resulting reactions were identical. That is, the fish extract also led to the threefold reaction. This reaction comprises:

- 1) a red spot of an approximately circular shape around the puncture due to local dilatation of the capillaries and venules;
- 2) a wheal over the same area due to a locally increased permeability of the vessel walls; and
- 3) a vivid scarlet flush, several centimeters in diameter, with irregular margins due to a reflex dilatation of the neighboring arterioles.

Lewis postulates that the triple response, which may be obtained by stimulation of the skin by chemical and by physical means such as heat, cold and light is caused by liberation in the skin of a histamine-like substance. Lewis and Grant conclude that the "anaphylactic poison" also acts on the skin by liberating in it an H-substance. Incidentally, Lewis' and Grant's paper is entitled "Notes on the anaphylactic skin reaction," not on the allergic skin reaction.

Hare's<sup>18</sup> findings were identical. He examined a pollen-sensitive and two horse-sensitive patients and found that horse extracts and pollen extracts also produced the three-fold skin reaction. These papers are especially important as they show that histamine plays a role in clinical allergy in humans and not only in experimental anaphylaxis in animals.

Between 1932 and 1939 a considerable number of workers adduced experimental evidence which leaves little doubt as to the correctness of Dale's theory. The following are the salient findings of these corroborative experiments:

- 1) During anaphylactic shock in the dog there appears in the blood and lymph a substance showing the biological characteristics of histamine.<sup>19</sup>
- 2) On perfusion of the isolated lungs of sensitized guinea pigs with a solution of the appropriate antigen there appears a histamine-like substance in the shock fluid which induces broncho-constriction in the lungs of normal guinea pigs.<sup>20</sup>
- 3) The active substance released during canine anaphylactic shock and from the shocked lungs of guinea pigs is inactivated by incubation with histaminase.<sup>21</sup>
- 4) A substance with the characteristics of histamine is released from various tissues of sensitized guinea pigs if the tissues are removed and shocked *in vitro*.<sup>22</sup>

5) Certain substances, which suppress the histamine contraction of plain musculature, also suppress their anaphylactic contraction. They do not, however, prevent the immunological stage of the reaction.<sup>23</sup>

6) During anaphylactic shock in dogs and guinea pigs there is a marked increase of the histamine content of the blood. In these latter experiments histamine was chemically identified as such.<sup>24</sup>

These findings cannot leave any doubt that histamine is released from the tissues during the anaphylactic reaction in animals and that it is responsible for the symptoms of anaphylactic shock.

For obvious reasons the evidence, which has been adduced to show that histamine is also responsible for the symptoms of clinical allergy, is more indirect and less comprehensive, but still very suggestive.

I have already mentioned the work of Lewis and his collaborators, in which they demonstrated that in atopic allergy the reaction of the skin to the specific allergen has all the earmarks of a reaction to histamine.

Certain individuals react to physical agents such as heat, cold, sunlight, with symptoms of hypersensitiveness such as asthma, vasomotor rhinitis, urticaria, angioneurotic edema.<sup>25</sup> This condition, which has been termed "physical allergy," is not based on an immunological mechanism. The work of Bray<sup>26</sup> and of Horton and his associates<sup>27</sup> has made it very probable that its symptoms are also caused by the liberation of preformed histamine from the tissues. In a boy suffering from cold allergy, Bray observed the triple response of Lewis, if the child's hands were immersed for a few minutes in water of 45 degrees Fahrenheit. In this experiment the patient's hands also became very itchy and swollen to more than twice their natural size. Several hours later the boy generally developed an irritating cough. In normal individuals Bray could provoke the characteristic triple response by immersion of the hands in water of 20 degrees Fahrenheit.

Horton, in collaboration with Roth and Brown,<sup>27</sup> described similar local and also systemic reactions to cold. The systemic reactions consisted of flushing of the face, a marked fall in blood pressure, a rise in pulse rate, and, frequently, development of syncope. Horton and Brown<sup>28</sup> further demonstrated that in a number of cold-sensitive individuals, immersion of the hand in water of 50 degrees Fahrenheit led to an increase of gastric acidity. Incidentally, Tinel<sup>29</sup> and his co-workers have reported increase of gastric acidity in serum-sensitive dogs on re-

injection of serum. All of the described reactions are typical reactions to histamine, and the assumption made by Bray and by Horton that these symptoms of physical allergy are caused by the liberation of histamine or of a histamine-like substance is very plausible.

As a point of special interest I should like to mention observations of Grant<sup>30</sup> and his co-workers, who were able to show that in cases of psychogenic urticaria the eruption was easily provoked by emotional stimuli, and also by exercise and warming the body. The explanation given by Grant is that, through stimulation of cholinergic nerve fibers, acetylcholine is released in the skin and that the acetylcholine in turn leads to liberation of a histamine-like substance.

In investigations on the pharmacological actions of pituitrin and its active constituents Fühner,<sup>31</sup> in 1912, found that it is possible to make rabbits tolerant to histamine. He injected increasing amounts and was able eventually to give doses which otherwise would have caused severe reactions. This observation was later to furnish the foundation for a new approach to the treatment of allergic diseases. Fühner's findings were verified and expanded by other workers<sup>32</sup> who were able to demonstrate that refractoriness to histamine can be induced also in other species, including humans.

The phenomenon of induced refractoriness to histamine has also furnished further proofs of the correctness of the histamine theory of anaphylaxis and allergy. In anaphylactic guinea pigs I<sup>33</sup> was able to show that the uterine strips of serum-sensitized animals, which had received histamine by injection or by mouth, were less sensitive to the specific antigen than were the sensitized uterine strips of the control animals, which had not received histamine. Miyamoto<sup>34</sup> had similar results.

In allergic humans Hare, whose work I previously mentioned, demonstrated that the skin of allergic individuals, if stimulated by the specific allergen, was rendered refractory alike to the allergen and to histamine. He further showed that if the skin was stimulated by histamine it was rendered refractory to the allergen.

We have traveled a long way since Dale in 1910 first recorded the belief—"as a point of interest and possible significance"—that the symptoms of anaphylactic shock are to a large extent those of poisoning by histamine.

The experimental observations, which since then have been made and which I have just presented to you, form the theoretical and prac-

tical basis of the histamine treatment of allergic diseases. The histamine theory would explain the symptoms of allergic conditions and why they are independent of the nature of the causative allergen and dependent only on the reaction of the shock organs. The possibility of inducing refractoriness to histamine, the substance responsible for the reaction of the shock organs, would reduce the treatment of allergic diseases to a common denominator.

Ramirez and St. George<sup>35</sup> were the first to use histamine in the treatment of an allergic condition. In 1924 they reported that they had used subcutaneous injections of histamine in the treatment of ten patients suffering from asthma due to "histamine sensitivity." These cases, which do not fit into the category of either atopic or physical allergy, remind one of the recent work of Horton<sup>36</sup> on "vascular headache." These headaches, which Horton attributes to histamine, are also alleviated by histamine injections.

In the sixteen years following Ramirez' and St. George's paper, there are but few reports in the literature on the use of histamine in allergic diseases. Friedlaender and Petow<sup>37</sup> applied it in various forms of migraine; Ernstene and Banks,<sup>38</sup> Gajdos,<sup>39</sup> Joltrain,<sup>40</sup> and Alexander and Elliot<sup>41</sup> used it in the treatment of urticaria; Collens and his associates<sup>42</sup> in the treatment of a case of insulin sensitivity.

Stahl and Masson,<sup>43</sup> Piquet,<sup>44</sup> Thiberge,<sup>45</sup> and Dzsini<sup>46</sup> used histamine in the treatment of bronchial asthma. Thiberge used it also in hay fever.

Bray<sup>26</sup> was able to achieve disappearance of the symptoms in his case of allergy to cold by injections of histamine, and Horton and his co-workers<sup>27</sup> later reported similar good results in the treatment of physical allergy.

The number of cases treated by these various workers is comparatively small, the time of observation relatively short. All of the authors, however, were impressed by the results achieved with histamine.

If histamine could be used successfully in the treatment of allergic diseases it would make for much simplification. Its use would be especially indicated in cases of multiple sensitiveness, in which several allergens would have to be used for specific desensitization, and also in cases which might be on an allergic basis in spite of the fact that a causative allergen could not be discovered. The physical allergies, as Bray and Horton have indicated, should also be amenable to histamine treatment.

These practical considerations and the soundness of the histamine theory have made us feel that the value of histamine therapy in allergic conditions should be intensively investigated.

For more than three years we therefore have been using histamine phosphate in the treatment of asthma, vasomotor rhinitis and hay fever in my clinic at Lenox Hill Hospital. We have been giving it by subcutaneous injection and have been following Dzsini's suggestion of using small doses. According to our opinion, the amounts used by the older workers (30 to 750 gammas per injection) are much too high. The initial dose in milder cases of asthma in adults is .1 gamma, in severe cases .01 gamma. In the preseasonal treatment of hay fever our initial dose has been .1 or 1.0 gamma. In children we always start with .01 gamma. In asthma and vasomotor rhinitis the maximum dose has been 50 to 75 gammas, in hay fever 100 to 200 gammas (in adults). The increase in dosage, the spacing of the injections and the number of injections given, depend on the patient's tolerance, age, and on the results achieved. Our detailed procedure and a discussion of our results and observations in asthma and vasomotor rhinitis are contained in a paper which is in press.<sup>47</sup>

The precautions to be taken are the same as in specific desensitization. However, we believe that histamine treatment causes less severe and less frequent systemic reactions than specific desensitization.

In the course of several thousand injections of histamine we have encountered systemic reactions in a few instances only. On one occasion a patient suffering from vasomotor rhinitis developed very severe headache two to three hours after the injection of .33 gamma. The headache lasted for about eighteen hours. In another case of vasomotor rhinitis the injection of 1 gamma brought on a severe attack of urticaria, which started at the site of the injection and persisted for several days. Two other patients, during the course of preseasonal treatment for hay fever, developed mild angioneurotic edema of the eyelids on several occasions after the injection of small amounts of histamine, and one of these patients on another occasion had urticaria. In view of these comparatively rare and not very severe systemic reactions, we feel that histamine would be indicated in such cases in which the patients react strongly to specific desensitization.

We have treated 105 persons with histamine. Sixty patients were suffering from asthma, vasomotor rhinitis, or both; their symptoms were



in most instances due to allergens other than pollens. The results of this treatment have been very satisfactory in a considerable percentage of the cases. In some instances the patients were not at all benefited. We were especially impressed by the fact that a number of patients suffering from severe asthma of long standing, and who had received specific desensitization treatment at the hands of very capable allergists, were greatly improved by histamine treatment.

I would like to present two successfully treated patients:

1) The patient, a six-year old girl, had had asthmatic attacks since she was fifteen months old. The attacks were especially severe during the winter; however, the patient had also occasional attacks during the summer months. During the last years the attacks had become more frequent and much more severe. The child had been laid up with asthma almost the entire winter of 1938 to 1939. The asthmatic attacks usually followed a head-cold. During August and September 1939 she had frequent attacks of urticaria. We first saw the patient last September. The physical examination was essentially negative. Skin-tests showed positive reactions to house-dust, cottonseed, ragweed and various grass pollens. Histamine treatment was started at the end of September. The initial injection in this case was .005 gamma. The dosage was increased very slowly and the injections were given throughout the fall and winter. The child had several colds during the course of the winter, and on one single occasion she had a very mild asthmatic attack, which lasted for a few hours only. The patient was last seen a few days ago; the dosage at this time was 15 gammas. The child's general physical condition is greatly improved; incidentally, she has gained ten pounds during the course of treatment.

2) The following case, which we had the opportunity of observing, represents, in our opinion, a direct experimental proof of the correctness of the histamine theory. The patient, a thirty-six year old baker, had been suffering from severe vasomotor rhinitis for the past three years. His attacks of paroxysmal sneezing and profuse watery nasal discharge occurred only in the bakeshop and only when he worked with wheat flour. The attacks would last for many hours. The patient gave a strong positive skin reaction to wheat extract. Histamine treatment was started with .1 gamma at the end of February 1938. Decided improvement was noted after the eleventh injection, which amounted to 3 gammas. Improvement continued and the patient was able to work without any

symptoms of rhinitis in April, May and June, during which time he was receiving injections of histamine. The last injection of 40 gammas was given at the beginning of July. The patient was able to work during the entire summer and had only infrequent, very mild symptoms. When we saw him in September he had been sneezing more frequently for about one week. He was given four injections of histamine and did not return for treatment, as he was improved. In July 1939, that is three-quarters of a year later, the patient reported that he had been working steadily with wheat flour since November 1938. He had been free from allergic symptoms during the entire time.

We have further treated persons with seasonal hay fever. Some of these patients received two or three courses of treatment with histamine during consecutive years. The results of this treatment during 1938 and 1939 are the following: Of a total of 48 patients, 21 were treated with very good, 12 with fair results; 15 patients had no benefit from the treatment.

From a theoretical point of view we are especially interested in the results achieved in hay fever as we are here dealing with a condition in which the clinical picture is usually clear cut, in which there are rarely complicating factors as in bronchial asthma, and in which the causative allergen can generally be ascertained with good precision. We are aware of the fact that the percentage of hay fever cases benefited by histamine treatment is not as large as that of cases receiving specific desensitization. This, we feel, is due to our not yet knowing the optimal dosage. The length of time we have been using histamine is short and one must consider how long it took to develop the optimal dosage for specific desensitization. At this stage we believe the essential point to be the fact that *qualitative* results can be achieved with histamine in the treatment of hay fever, which compare absolutely with those achieved with specific desensitization.

In our opinion histamine therapy is destined to mark a further advance in the treatment of allergic diseases. Much experience will be needed before a final verdict can be given, and it has been the objective of this presentation to stimulate other workers to help procure it.

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## AN AMERICAN PRECURSOR OF FREUD\*

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TO MOST people, doctors included, Freud's name is associated with sex. Of all the new and revolutionary concepts that he introduced into the mental and allied sciences, none are as conspicuous as his theories on the role of sex in normal and abnormal life. Before I introduced Freud here, I was well aware that there was considerable opposition to his sexual theories. I witnessed many of these controversies abroad while I was a member of Eugen Bleuler's staff at Burghölzli, Zurich, the first psychiatric clinic which opened its doors to Freud. I was, therefore, pleasantly surprised at the sympathetic reception of my first paper on Freud's theories, which I presented before the Section of Neurology and Psychiatry of this Academy on October 11, 1909.<sup>1</sup>

This pleasant feeling, like all emotions of this nature, did not last very long; the resistance to Freud's teachings kept on increasing and reached a high level soon after the appearance of my translation of his *Three Contributions to the Theory of Sex*.<sup>2,3</sup> As his sole representative here, I naturally became the principal target for all the senseless and foolish attacks that were directed at Freud. But, somehow, I could not take these criticisms seriously, for I knew that long before Freud was on the scene, neurologists and psychiatrists had more than an inkling concerning the role of sex in the neuroses. They frequently advised marriage for hysterical, schizophrenic and other psychotic women on the assumption that sex would cure their maladies. I also recalled that while I was a medical student, the professor of neurology and psychiatry, M. Allan Starr, taught us that sexual excesses played a part in the etiology of organic and functional nervous diseases, despite his present objection to Freud's views. As a matter of interest, I then examined the pre-Freudian psychiatric literature and found that every textbook on nervous and mental diseases which appeared in the 19th century and in the beginning

\* Given March 13, 1940, before the Section on Historical and Cultural Medicine of The New York Academy of Medicine.

of this century, numbered sexual abuses among the etiological factors of the neuroses and psychoses. One finds plenty of sexual material in the works of Esquirol, Maudsley, Griesinger, William and Graeme Hammond, Spitzka, Handfield, Bandy and Krafft-Ebing. T. S. Clouston,<sup>4</sup> who wrote in the beginning of this century, describes uterine or amenorrheal insanity, ovarian or "old maid's insanity," and insanity of masturbation; and in 1911 Church and Peterson gave masturbation and sexual excesses in the general etiology of insanity.<sup>5</sup> In view of all this, I concluded that we dealt with two classes of critics—those who were actuated by some personal complex and those who were honest seekers after the truth. The former were incapable of conviction, while the latter, who objected to Freud's interpretations of neurotic symptoms on a sexual basis, invariably gave up their opposition as soon as they understood Freud's theories of sex. I fully sympathized with this class of critics, for I knew that no one had hitherto interpreted psychoneurotic symptoms sexually. But, said Koheleth: "And there is nothing new under the sun."

While returning from a trip abroad on the *Normandie*, in 1936, I had the pleasure of meeting the late President of the Borough of Brooklyn, Mr. Raymond V. Ingersoll, whom I had known personally for some years. During one of our promenades on deck, I learned with interest that he was the son of a physician, that his father had specialized in the treatment of nervous diseases and that he anticipated some of the theories which were later advanced by Professor Freud. As a result of this conversation, and later investigation, I shall now present something of the life and theories of Dr. A. J. Ingersoll, founder of the Pinewood Sanitarium of Corning, New York. I might begin by saying that after reading his book, entitled: *In Health*,<sup>6</sup> and from personal information obtained from his distinguished son, who died only recently, I feel that Dr. Ingersoll was in many respects the American forerunner of Freud.

Dr. Andrew J. Ingersoll was born in 1818, near Hammondsport, New York, and died in Corning, New York, in 1893. He came from a long line of New England ancestors. His father was an energetic farmer near Lake Keuka, a Jackson democrat, and a strong Presbyterian. The family was large, and Andrew had little opportunity of getting even a common school education. From early life he became habituated to the hard and steady labors of the farm, but he always showed a strong curiosity for knowledge and spent most of his leisure time in reading. He seemed to have been early impressed by the mysteries of life; as he puts

it: "From my earliest recollection a desire to comprehend human life possessed me."<sup>6</sup> At the age of 24 he resolved to prepare himself for the ministry, but he soon became confused by theological problems, and after some struggle he gave up the idea of becoming a preacher.

It is interesting to note that his doubts revolved around the question of the origin of God. He states that he believed that every design must have a designer, and he could not comprehend who was the designer of God himself. It was this obsessive rumination which finally forced him to abandon the ministry and "to disbelieve everything which my unregenerated rational nature could not understand."<sup>6</sup> We learn that he was then called an infidel, that he did not believe in Christ, nor that the Bible was the word of God, but he did believe that there was a God.

Those conversant with psychoanalytic thought will readily understand the meaning of such a conflict. It is always based on a phase of early infantile sexual investigation, which usually comes to an end through some energetic sexual repression. Behind such obsessive ruminations, there is always the question: "Where did I come from, how was I born?" In a distorted way it is represented by the well known riddle of the Sphinx.<sup>3</sup> Judging by many similar cases and by the issues of this case, which will be presently shown, it is safe to assume that the young theological student's obsessive doubts were based on a repressed infantile sexual investigation; that the early sexual curiosity became more or less inhibited through religious forces; and that the repression later broke through and came to the surface as the obsessive question about the origin of God.

But experience teaches that such a psychic crisis is never monosymptomatic. One would, therefore, expect to find other symptoms besides the doubts mentioned. That this was actually the case is confirmed in his biography, where we read that in addition to his religious entanglement, there was an internal unrest and discontent, together with some troubles at home, which reduced him to sickness and unfitted him for active work.<sup>7</sup> Our future psychotherapist evidently went through a conflict on the basis of an unresolved Oedipus situation, which must have raged within him for some time. His final resolve to become a physician, "to be of service to the sick," as he puts it, was undoubtedly influenced by his Quaker mother, of whom we are told that she was always in demand wherever there was sickness or other trouble.<sup>6</sup>

To become a physician was not so difficult in those times. In 1842-43



there was no Board of Regents; anyone so inclined, particularly in rural communities, could take up the practice of medicine. It is to be noted, however, that years later when the practice of medicine in New York State was legalized, Dr. Ingersoll was duly licensed on his record, so that for about 20 years before his death he was a legal practitioner of medicine in this State.

That the former theological student solved his neurotic conflict by becoming a physician is especially interesting. He evidently had considerable insight into his own state; he knew he was ill and that his sickness was caused by mental and spiritual strife. He took up mental healing because unconsciously or consciously he wished to heal himself. From the very beginning of his career Dr. Ingersoll's interest was centered on the sexual and on the mental processes. He never used medications; he was what they called a "drugless physician." Besides hydrotherapy, which he administered rather crudely, he relied entirely on psychic measures. He believed that there is a natural curative power or tendency in the human body, which does the work of restoration, and that he had the power to promote it. He first discovered that he could relieve headaches and other complaints with his hands,<sup>7</sup> and then he developed the method of "hanging the head" therapy, which consisted of a "simple dropping of the chin upon the breast, accompanied by a complete relaxation of body and mind." He claimed and demonstrated through many cases that physical strength was rapidly regained by such relaxation and surrender of will. That such simple treatment should have been efficacious will surprise no one who knows anything about suggestive therapy. For it is not the method, but the personality behind it that cures.

Dr. Ingersoll was very eager to give others the benefit of his experience without any compensation, but at first he confined his treatment to men only. As time went on, his system underwent a definite modification and gradually assumed an eroto-religious character. He tells us that for a number of years after he became a psychotherapist he had no definite religious belief, nor did he understand the power by which he cured the sick. One gathers that his internal struggle continued unabated in the form of a tension between the *Ego* and the *Superego* of his mental personality.<sup>8</sup> On the one hand, he rejected religion; on the other hand, he could not dismiss the thought that he was *not* religious. In addition to the religious conflict, he displayed a marked sensitiveness towards the problem of sex. This came to a climax when a friend asked him to treat

his wife, who was seriously ill. Dr. Ingersoll states that he was anxious to help the woman, but fearing lest in his treatment he would have wrong thoughts towards her, he refused the case. But as his friend persisted in begging him to help his wife, Dr. Ingersoll finally consented to consider the matter. That night while "hanging his head," something from within seemed to say, "If you surrender your will in deep desire for help, I will keep you pure in thought. Something within seemed to assure me that He would protect me if I would trust my sexual nature to His care. I did so and His promise was fulfilled."<sup>6</sup> Here, we get a glimpse of the deep struggle between his primitive and ethical nature, *i.e.*, between his *Ego* and the *Id*.<sup>8</sup> He was evidently afraid of trusting himself with women and strove to master the mechanism of transference, concerning the force of which we have learned so much from Freud. It is remarkable that although untutored in normal and abnormal psychology and under the stress of a deep conflict, Dr. Ingersoll not only frankly recognized this force, but also controlled it properly through sublimation by surrendering to the commands of the *Superego*, which he naturally conceived as the Holy Spirit. Thus, his conflict between his sexuality and religion was settled on a basis of compromise. By identifying his own conflicting tendencies with those of his patients, he was able to sublimate his libido on a basis of religion, and thus hold in check the schizoidism which threatened to undermine his personality. However, the final adjustment of his sexual life was probably not effected until the age of about 43, when he married one of his patients, Miss Ellen S. Vail, the daughter of an old Quaker family, with whom he begot seven children, six of whom grew up into useful and distinguished citizens.

Before proceeding to illustrate to what extent we are justified in calling Dr. Ingersoll an American forerunner of Freud, I wish to forestall some arguments that may be brought against this assumption. I have already stated that Dr. Ingersoll had no medical or any other standard education, in our sense of the term; he was, as it were, a self-made psychotherapist, while Professor Freud we know was one of the most educated, learned, medical men of his time. There is, therefore, no comparison between these two men in this respect. The Freud whom we have in mind when we speak of Dr. Ingersoll as his precursor, is the developer of the mechanisms of the *unconscious*, of *repression*, *sublimation*, *transference*, *resistance*, and last, but not least, the discoverer of the great part that *sex* plays in the neurotic symptoms. Making due allowances, there-

fore, for the differences in the backgrounds of the two men, it is, nevertheless, very remarkable that without any medical or other education to speak of Dr. Ingersoll should have perceived and expressed these mechanisms, no matter how simple and crude they sound in comparison to Freud's scientific elaborations.

In 1896 Freud said: "In a normal sexual life no neurosis is possible." In 1877 Dr. Ingersoll said: "From my experience in ministering to the sick, I believe that disease originates in unregenerated sexual life."<sup>6</sup> Freud repeatedly insisted that sex is an integral part of the individual and must be considered as a basic part of normal or abnormal behavior. Dr. Ingersoll states: "We are so constituted that we cannot look with a condemnatory spirit upon any part of our organism, without creating disease in that part; showing clearly that 'a house divided against itself cannot stand.'"

According to Freud only a small part of sex is lived through in the primitive sense; the rest must be *sublimated* or deflected to higher social or esthetic aims. Dr. Ingersoll says: "All sensations of sexual feeling should be committed or yielded to Christ. To do this there should be thankfulness for it, and mercy and good will towards it, at the moment there is consciousness of it."<sup>6</sup> In other words, it is not a surrender of sex in an ascetic or monastic sense, but in an exaltation of the body.

All medical authors who wrote about unconscious mental activity invariably spoke of the "subconscious"; Dr. Ingersoll always speaks of the *unconscious*, a term exclusively used by Professor Freud and his School. Speaking of the unconscious manifestations of resistance, he states: "Fear of conception causes rigidity of the *constrictor vaginae* muscle, and through this rigidity all the muscles become tense, creating more or less soreness in the whole body."<sup>6</sup> In a simple way Dr. Ingersoll expresses here the Freudian mechanisms of *conversion* and *displacement*, the meanings of which are too well known to need further elaboration.

Dr. Ingersoll's formula for the treatment of such cases is expressed in the following sentence: "All who thus suffer, should desire sexual life, and reverence and gratitude for every consciousness of it." The psychotherapist of today would not be so sure that "Then the muscles will relax and the suffering cease,"<sup>6</sup> as soon as the patient would accept the interpretation. We often know the meaning of the symptoms after a short period of study, but it requires many hours, weeks or months before the patient is capable of accepting the unconscious meanings of

the symptom. However, Dr. Ingersoll was well aware that his interpretations were not always accepted by his patients. He tells us that notwithstanding his many successes, he was unable to lead many of them to seek the redemption of their souls by commitment of their sexual life to Christ, "because Christians generally believe that this infection of nature doth remain, yea in them that are regenerated." He refers here to the ninth article of religion as expressed in the Episcopal Church.<sup>6</sup>

But the doctor was so profoundly convinced of the correctness of his theory that whenever the patient did not recover, or died, it never occurred to him to question his diagnosis. Thus, he cites the case of a lady who for several years had frequent nocturnal attacks of "suppression of the breath," which he interpreted as an effort on her part to crush all her sexual feelings. He told the patient that if she did not stop the effort to suppress her sexual life, she would die in one of these attacks. The patient apparently "insisted that sexual desire was wrong and that she would rather die than have any such feeling."<sup>6</sup> One night the doctor called to see the patient and found her struggling for breath, and she died in a few minutes. Dr. Ingersoll states: "I can give no other explanation of her disease than that it was caused by the action of the will as described above."<sup>6</sup>

The Doctor tells us nothing of the patient's physical condition; it never occurred to him that death may have been caused by some pulmonary, cardiac, or other physical malady. Still, the doctor's diagnosis may have been essentially correct. Death can be produced by a strong "will to die." We have convincing reports from many competent and reliable observers that primitive people can die at will, and I have shown that people of a neurotic constitution sometimes depart from life in a similar manner.<sup>9</sup> Dr. Ingersoll seemed to have perceived this idea when he states: "The unconscious action of the will occasioned by fear seems to take possession of the body,"<sup>10</sup> and then gives the cases of two patients who became debilitated by the will acting *unconsciously*\* upon their voluntary muscles as a result of their bitter condemnation of the men who made impure proposals to them. One recovered after she forgave the man while the other would not forgive and died soon after leaving his care.<sup>6</sup> We need not agree with Dr. Ingersoll to be impressed by his anticipation of Freud's concept of unconscious mental activity.

That he considered sex in the broader sense of the Freudian *libido* is

\* Italicized by writer.

shown by the following passages: "Sexual life, God's sustaining life in man, is not simply the life of the organs to which He has assigned the most important office of bringing into existence immortal souls." Dr. Ingersoll then goes on enumerating the wide ramifications of sex and ends with the following sentence: "It gives motion to the muscles and life to the nerves, and controls all the actions of humanity."<sup>6</sup>

When one reads his cases, his clinical material, one is still more impressed by the fact that he perceived many of the mechanisms which were later developed by Freud and his pupils. It is more than doubtful that Dr. Ingersoll was influenced by Plato, who first associated hysteria with sex suppression.\* As far as we know, Freud was the first modern investigator to give expression to it. But in 1877 Dr. Ingersoll stated that "hysteria is frequently caused by the voluntary suppression of the sexual life."<sup>6</sup> He gives a number of cases to substantiate this statement, of which the case of Miss C. is a typical example. She was unable to move, speak, or even whisper, and had not menstruated in 18 months. He told her that she had no organic disease, but that her condition was due "to anger at her catamenial function." She finally admitted the truth of his diagnosis, became reconciled to menstruation as the divine will in her being, and soon recovered.

Dr. Ingersoll disagreed with Drs. Clarke, Maudsley, and others that study during menstruation produces disturbances in the female functions. He said, "While the light of physiology is not to be rejected, it should not be accepted as the standard of the effects of study upon females."<sup>6</sup> All patients who accepted his religious views on this function performed physical or mental work during these periods without any inconvenience.

He gives many instances of various forms of hysteria, the sexual bases of which he correctly diagnosed. He states that the patients were cured when they accepted sex as a natural and divine gift.

The case of Mr. J.,<sup>6</sup> who was addicted to self-abuse and subject to seminal emissions, is particularly interesting. For years this patient struggled with his sex, consulted an eminent physician, who treated him by medications, attributed his seminal emissions to cerebral congestions, and told him that the emissions were "the work of nature to relieve the pressure on his brain, and unless he had them, he might have had apoplexy." After eight years of severe suffering, Mr. J. consulted Dr. Inger-

\* Plato's matrix theory of hysteria is nicely described in his *Timaeus*.

soll, who told him that his trouble was spiritual, that it was due to a wrong conception of the relations of his bodily to his spiritual powers. "All your life," said the doctor, "you have been sorely grieved and well nigh angry with yourself that you were a man. The feeling and powers of sex which make you distinctly a man, you have never reckoned holy in Christ, nor redeemed by him." Dr. Ingersoll advised his patient to stop worrying and commit his sexuality to Christ, who would control it for him. In other words, he removed the conflict by showing the patient that sex is a natural God-given function, of which one need not be ashamed or afraid.

The case of Miss I. is also worthy of a brief description.<sup>6</sup> This patient, a young married woman, consulted Dr. Ingersoll after she had been diagnosed as scrofulous and pronounced incurable by her physician. "When she came to me," Dr. Ingersoll states, "she was invariably nauseated after taking food, was unable to walk without a crutch, and frequently fainted in trying to cross a room." Investigation showed that her ailment began shortly before her marriage when she brooded over the idea that no wife could be pure if she had any enjoyment in sexual intercourse. She was determined not to allow marriage to create in her any sexual desire, and she had religiously adhered to this determination with entire success. Dr. Ingersoll told the patient that the want of sexual life was the cause of her illness, that she elevated everything except sex, which she thought low, that she had set up in her heart a false standard of purity, and that the sexual desire of her husband was not animal, as she thought, but given by God to woman as well as to man. After she became convinced, and acknowledged that God could bestow nothing that was impure, she felt that her husband had been purer than she. Her appetite then improved and she soon discarded the crutch and within a few weeks could walk four or five miles over rugged hills without lameness or fatigue. Dr. Ingersoll adds: "It is now five years since she was cured, and she still appears to enjoy perfect health, having in that time never been ill a day."

The report of this case sounds very simple in comparison to our present day case records. But we must not forget that the patient was diagnosed and treated as having an organic disease and that Dr. Ingersoll had the insight to diagnose the disease as hysteria on the basis of a psychosexual disturbance and cured the patient by his system of therapy. We could quote similar instances of hysteria from our present

day practice, in patients who were diagnosed and treated as having organic disease which turned out later to be functional. But in the '70s and '80s of the last century, things were quite different. At that time most of the reputable neurologists and psychiatrists considered hysterical symptoms as manifestations of some local cerebral irritations. When this case was reported, Freud was not yet a medical student.

Dr. Ingersoll was firmly convinced that "the physician of the soul was the healer of the body,"<sup>6</sup> and for that reason, as well as for lack of training, he now and then made mistakes. Thus, he gives the case of a young lady who had lost her voice. Dr. Ingersoll diagnosed her aphonia as a repugnance which she felt towards becoming a mother, and when he told this to the patient, she whispered that if she should ever marry a good husband, he would not wish her to have children. He ends up by saying that she could not be convinced of the truth, and died in a few months of consumption. There is no doubt that this patient had a distorted view of sex and that hysterical symptoms often develop in such predisposed persons, but to the medically trained psychotherapist, it would seem that Dr. Ingersoll dealt here with a case of tuberculosis of the larynx.

At all events, Dr. Ingersoll was the first American physician to my knowledge who stressed the sexual factors in the neuroses. He was a truly religious man, who, having been influenced by his Quaker mother, set out to serve mankind. His own sexual struggles showed him the psychogenesis of the neuroses long before Freud discovered and described them. His method of treatment consisted of a mixture of religion and crude science. When one reads his book, one sees that he was influenced by his times, when many people were still under the spell of the Fox sisters, who brought spirit mediums into vogue. Dr. Ingersoll diagnosed a few cases as spirit mediums, but rejected spiritualism as well as mesmerism and hypnotism, as "evils very dangerous to the soul."<sup>6</sup> In the light of our present knowledge his method of treatment consisted mainly of suggestion and interpretation; the former was of a religious while the latter was of an erotic nature. The only ceremonial that he inaugurated into his treatment was "head-hanging," which he described as follows: "To relax the nervous and muscular systems is to drop the head towards the chest, to sit with every muscle relaxed, sometimes for hours, and to let go all will over the muscular systems, just as you have seen people do when asleep in their chair."<sup>6</sup> He states that the mental condition during

this posture was expressed by Wordsworth in these words:

"In such high hour  
Of visitation from the Living God  
Thought was not."

It is, according to Dr. Ingersoll, a complete yielding to Christ, to whom all sensations of sexual feelings are thus committed. He firmly believed that Christ revealed to him the second birth through his sexual life by giving him love and reverence for it.<sup>5</sup> He dilates upon this thought by quoting the words of Paul: "I am crucified with Christ; nevertheless, I live; yet not I, but Christ liveth in me." (*Galatians* II:20) This mystical identification with Christ—that is, a direct union with God, the aim of all mystics, was also experienced by Dr. Ingersoll. But, we know that mysticism furnishes the clearest examples of the influence of the mind on the body, and that belief is the most ideal therapy in psychic disturbances. Unfortunately, such suggestive therapy is at best of a transient nature. Dr. Ingersoll's personality shows much of the religious mystic and his therapy was undoubtedly based on a profound conviction that he represented Christ, the healer. He did not, however, depend on this alone. In addition to his deep conviction, which he imparted to his patients, he also resorted to the interpretation of the symptoms on a psychosexual basis. In this he not only anticipated Freud, but in a crude way he perceived and described many of the psychoanalytic concepts.

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## LIBRARY NOTES

AN EXHIBITION OF BOOKS SHOWING SOME  
CONTRIBUTIONS TO OUR KNOWLEDGE OF  
THE THYROID AND PARATHYROID GLANDS\**Prepared by*

ANGELA WHITE

Assistant in the Rare Book and History Room

## THE THYROID AND ITS ABSENCE OR DEFICIENCY

1. Plinius Secundus, Caius (the elder). 23-79.

The historie of the world. Commonly called, the naturall historie . . . Translated into English by Philemon Holland.

London, 1601, opened at p. 339.

As early as the first century goiter was noted in men and swine. Pliny attributed it to the drinking water.

2. Juvenal. ca. 60-130.

The satires of . . . no. 13.

In: Juvenal (ca. 60-130) & Persius (34-62). [*Satires*]. Literally translated by the Rev. M. Madan. Princeton, 1850, opened at p. 102.

"Who wonders at a swoln throat in the Alps?"

From this we can assume that goiter was endemic in the Alps in the first century.

3. Celsus, Aurelius Cornelius. 1st. cent.

De medicina.

Venice, 1493, opened at fol. xlviii verso.

An account of cystic goiter. In its treatment with caustics the author says "sed scalpelli curatio brevior est". Though the thyroid was not recognized

at the time as normal equipment of the body, this is considered the earliest reference to its surgery.

4. Galen. ca. 129-200.

Opera . . .

Basileae, 1542, vol. 7, opened at p. 230.

A rather vague account of the thyroid. The author considered its secretion a lubricant for the larynx and its cartilages for the facilitation of speech.

5. Paulus Aegineta. 625-690.

Opus de re medica . . .

Paris, 1532, opened at p. 21.

The author recommends surgery for the treatment of goiter.

6. Abulcasis. 1013-1106.

De chirurgia. Arabice et Latine. Cura Johannis Channing.

Oxonii, 1778, vol. 1, opened at p. 229.

The author, whose works are based on those of Paulus Aegineta, has been spoken of as the first to operate for goiter, though we know that as early as the first century Celsus made a reference to goiter surgery. Abulcasis may have been the first actually to perform an operation, however. He calls the dis-

\* Held in conjunction with the Graduate Fortnight on "The Endocrine Glands and their Disorders," Oct. 23 to Nov. 3, 1939.

- ease elephantiasis of the throat. It is interesting to note that he had observed its frequency in women.
7. Arnoldus de Villanova. d. 1311.  
Opera omnia. Cum Nicolai Taurelli . . . annotationibus . . .  
Basileae, 1585, opened at p. 1190, De botio gulae, cap. 4.  
A medieval discussion of the medical treatment of goiter. He recommends burnt sponge as a therapeutic measure.
8. Polo, Marco. 1254-1323?  
The travels of . . .  
London, [1931], opened at p. 65.  
"They mostly have goitres, and this is due to the nature of the water they drink."  
In his travels in China the author observed the prevalence of goiter at Yarkand. Like so many before him he considered it due to the drinking water. Borrowed through the kindness of the New York Public Library.
9. Guy de Chauliac. d. 1368.  
Here bigyney ye inventorie or ye collectorye in chirurgicale parte of medicine compiled and complete i ye yere of oure lord, 1363 . . .  
[England? 14—?], opened at fo. 43 recto.  
Manuscript in English of the author's *Chirurgia magna*, 1363, the only English translation of Guy de Chauliac that is known. He advocates extirpation of goiter.
10. Leonardo da Vinci. 1452-1519.  
I manoscritti di Leonardo da Vinci della Reale biblioteca di Windsor. Dell'anatomia fogli A . . .  
Parigi, 1898, opened at fo. 3 recto.  
Drawing of the thyroid gland. On p. 74 da Vinci says that these glands were made to fill in where the muscles were lacking and that they separated the trachea from the collar bone.
11. Leonardo da Vinci. 1452-1519.  
[Drawing of a monster with two large goiters].  
In: Clark, (Sir) Kenneth. *A catalogue of the drawings of Leonardo da Vinci in the collection of His Majesty the King at Windsor Castle*. N. Y. & Cambridge [Eng.], 1935, vol. 2, opened at no. 12371.
12. Michelangelo. 1475-1564.  
"I' ho già fatto un gozzo."  
In: Symonds, John Addington. *Rennaissance in Italy: the fine arts*. New ed. London, 1899, opened at p. 379.  
"I've grown a goitre by dwelling in this den—  
As cats from stagnant streams in Lombardy,  
Or in what other land they hap to be—"  
A sonnet written by Michelangelo while he was painting the roof of the Sistine Chapel in 1508. The first three lines suggest water as the cause of goiter. Borrowed through the kindness of the New York Public Library.
13. Paracelsus, Aureolus Philippus Theophrastus. 1493-1541.  
Opera omnia . . .  
Ed. nov. Genevae, 1658, vol. 2, opened at p. 382.  
He seems to be the first to point out a relationship between goiter and the form of congenital idiocy known as cretinism. (This was published as early as 1567 in his *Philosophiae magnae* . . . Cöln, pp. 139-156.)
14. Vesalius, Andreas. 1514-1564.  
De humani corporis fabrica libri septem.  
Basileae, 1543, opened at p. 256.  
Drawings of the thyroid.
15. Platter, Felix. 1536-1614.  
Praxeos medicinae tomi tres . . .  
Basileae, 1625, vol. 1, opened at p. 80.  
An early description of cretinism from the point of view of mental deficiency. The relationship between cretinism and goiter is also brought out. The first volume of the first edition of this work appeared in 1602.
16. Shakespeare, William. 1564-1616.  
The tempest.  
N. Y., [19—?], opened at act III, scene III, p. 68.  
Gon.: "Who would believe that there were mountaineers  
Dew-lapp'd like bulls, whose throats  
had hanging at them  
Wallets of flesh; or that there were  
such men  
Whose heads stood in their breasts?"  
The poet's picture of goiter and cretinism.

17. Wharton, Thomas. 1614-1673.

*Adenographia* . . .

Londini, 1656, opened at p. 118, cap.

18, *De glandulis thyroidoicis*.

The author described the thyroid more accurately than his predecessors and gave it its name in 1656. He noticed the vascularity of the organ, and thought one of its functions was to fill up the spaces around the larynx, thus contributing to the beauty of the neck. He considered this particularly true in females, which accounted for their larger thyroids.

18. Hocfer, Wolfgang. 1614-1681.

*Hercules medicus* . . .

Viennae, [1657], opened at p. 37.

An early account of cretinism, attributing it to faulty habits of diet and mode of living.

19. Gibson, Thomas. 1647-1722.

*The anatomy of humane bodies epitomized* . . .

2. ed. . . . London, 1684, opened at p. 332.

The author seems to consider the function of the thyroid to improve the appearance of the neck, and its secretion to lubricate the larynx "whereby the voice may be made more smooth and sweet".

The first edition of this work appeared in 1682.

20. Cowper, William. 1666-1709.

*The anatomy of humane bodies* . . .

Oxford & London, 1698, opened at table 24.

The author considered the thyroid gland "to be of the same office with the thymus". The latter he classed as a lymphatic gland. Though the text is Cowper's own, most of the plates (including that of the thyroid) are from Bidloo's *Anatomia* . . . Amsterdam, 1685.

21. von Haller, Albrecht. 1708-1777.

*Physiology* . . .

London, 1754, vol. 1, opened at p. 258.

The author doubts the existence of ducts connecting the thyroid and trachea, at a time when those ducts were accepted as an established fact.

22. Wilmer, Bradford.

Cases and remarks in surgery: to which

is subjoined, an appendix, containing the method of curing the bronchocele in Coventry.

London, 1779, opened at p. 251.

The "Coventry Treatment" for goiter, which introduced the burnt sponge remedy into England. This remedy had been a secret in the possession of a family at Coventry for many years. The treatment must be undertaken when the moon is full. It is amusing to note on p. 238 a quotation from Girard illustrating the almost universal appearance of goiter in the Tyrol. It was said of an English traveller that he would have been a handsome man if only he had had a goiter.

Borrowed through the kindness of the Army Medical Library.

23. Courtois, Bernard. 1777-1838.

*Découverte d'une substance nouvelle dans le vareck*.

In: *Annales de chimie*, Paris, 1813, vol. 88, opened at p. 304.

The discovery of iodine.

Borrowed through the kindness of the New York Public Library.

24. Coindet, Jean François. 1774-1834.

*Découverte d'un nouveau remède contre le goître*.

In: *Annales de chimie et de physique*, Paris, 1820, vol. 15, opened at p. 49.

Though iodine-containing substances had been used for centuries in the treatment of goiter, this is the first use of iodine alone. The author reports successful results.

Borrowed through the kindness of the New York Public Library.

25. King, Thomas Wilkinson. 1809-1847.

*Observations on the thyroid gland, with notes on the same subject by Sir Astley Cooper*.

In: *Guy's hospital reports*, London, 1836, vol. 1, opened at p. 443.

The author, who has been called "the father of endocrinology," seems to have anticipated the endocrine action of the thyroid in 1836. On p. 441 he says, "Whilst the nourishment of a part is indispensable to its existence; the influence which it exerts upon the circulating fluids may be more or less need-

ful for the healthful subsistence of the entire animal." And on p. 443, "Yet we may one day be able to shew, that a particular material principle is slowly formed . . . in the course of the circulation." This seems to show he had a conception that internal secretions are poured into the blood stream for general distribution.

26. Norris, Hugh. 1820-1910.

Notice of a remarkable disease, analogous to cretinism, existing in a small village in the west of England.

In: *Medical times*, London, 1848, vol. 17, opened at p. 257.

An instance of endemic cretinism in England in 1847. The author considers that the disease may be caused by the goiter which usually accompanies the condition. He also expresses the belief that its cause is a combination of circumstances, among them intermarriage, inferior water and impure air.

27. Curling, Thomas Blizard. 1811-1888.

Two cases of absence of the thyroid body . . .

In: *Medico-chirurgical transactions*, London, 2. ser., 1850, vol. 15, opened at p. [303].

In 1849 the author discovered an absence of the thyroid gland in two cases of cretinism. He is the first to suggest that the cretinism may be due to thyroid deficiency.

28. Chatin, Gaspard Adolphe. 1813-1901.

Existence de l'iode dans les plantes d'eau douce . . .

In: *Compt. rend. hebdomadaire des séances de l'Académie des sciences*, Paris, 1850, vol. 30, opened at p. 352.

The first of a series of contributions demonstrating the relationship between iodine deficiency in water, soil, plants, etc. and endemic goiter. He was not the first to put forth this theory, but his were the first extensive investigations carried out. He recommended adding iodine to the water supply as a prophylactic measure. His advice was not accepted, and it was over seventy years later before a similar investigation was carried out which confirmed his theory.

29. Schiff, Moritz. 1823-1896.

Untersuchungen über die zuckerbildung in der leber . . .

Würzburg, 1859, opened at p. 61.

An important contribution which was overlooked for more than a quarter of a century. The author totally extirpated the thyroid glands of dogs with the result that death followed. Neither Reverdin nor Kocher appeared to be aware of Schiff's work when they published their results of complete thyroidectomy.

Borrowed through the kindness of the Army Medical Library.

30. Sick, Paul.

Ueber die totale exstirpation einer kropfig entarteten schilddrüse . . .

In: *Med. corresp.-blatt* . . . Stuttgart, 1867, vol. 37, opened at p. [199].

He is credited with being the first to notice symptoms of loss of thyroid function following thyroidectomy. Whether he was the first to extirpate the gland completely has been debated. Halsted considered it the first total excision and "the first report of the condition which we now recognize as status thyreoprivus."

31. Saint-Lager, J.

Études sur les causes du crétinisme et du goître endémique.

Paris, 1867, opened at p. 245.

He tells us that the people of Lausanne carried small bottles of iodine around their necks like amulets, in an effort to protect themselves against goiter. This was in 1867. Walter M. Boothby, in 1935, considered this to be a reasonably good prophylactic measure in the light of recent knowledge.

32. Fagge, Charles Hilton. 1838-1883.

On sporadic cretinism, occurring in England.

In: *Medico-chirurgical transactions*, London, 2. ser., 1871, vol. 36, opened at p. 154.

The author pointed out the similarity and differences of symptoms in sporadic and endemic cretinism. His suggestion that cretinism might occur in adult life and the symptoms he thought would attend it were confirmed by Gull in 1873.

33. Gull, (Sir) William Withey. 1816-1890.  
On a cretinoid state supervening in adult life in women.  
In: *Trans. Clinical soc. Lond.*, 1874, vol. 7, opened at p. 180.  
The classic account of myxoedema is due to Sir Wm. Gull in 1873. He called it "A cretinoid state" to which Ord in 1877 gave the name myxoedema.
34. Ord, William Miller. 1834-1902.  
On myxoedema, a term proposed to be applied to an essential condition in the "cretinoid" affection occasionally observed in middle-aged women.  
In: *Medico-chirurgical trans.*, London, 2. ser., 1878, vol. 43, opened at p. [57].  
In 1877 the author gave myxoedema its name. He did not recognize myxoedema and cretinism as the same condition occurring at different stages of life, but on p. 72 he suggests that the same cause may be in operation at the beginning of each.
35. Bourneville, Désiré Magloire (1840-1909) & d'Olier, H.  
Note sur un cas de crétinisme avec myxoedème . . .  
In: *Progrès médical*, Paris, 1880, vol. 8, opened at p. 709.  
These authors are said to be the first to recognize cretinism and myxoedema as the same condition. They state, "il [myxoedème] apparaît comme complication d'un état préexistant: le crétinisme; il semble en quelque sorte remplacer le goitre absent". In 1883, Felix Semon contended that cretinism, myxoedema and cachexia strumipriva were all due to lack of thyroid secretion.
36. Reverdin, Jacques Louis. 1842-1929.  
[Accidents consécutifs à l'ablation totale du goitre].  
In: *Revue médicale de la Suisse romande*, Genève, 1882, vol. 2, opened at p. 539.  
The author is considered the first to report that a syndrome as of myxoedema follows complete thyroidectomy in human beings. However, Schiff, in 1859, told of fatal results following complete removal of the thyroid in animals.
37. Kocher, Theodor. 1841-1917.  
Ueber Kropfexstirpation und ihre folgen.  
In: *Archiv für klinische chirurgie*, Berlin, 1883, vol. 29, opened at p. [254].  
A verification of the work of Reverdin that a syndrome resembling myxoedema followed complete removal of the thyroid in human beings. Kocher called this condition "cachexia strumipriva."
38. Semon, (Sir) Felix. 1849-1921.  
[Discussion on a case of myxoedema presented before the Clinical society of London, Nov. 23, 1883].  
In: *Brit. med. jour.*, London, Dec. 1, 1883, opened at p. 1073.  
The first suggestion that cretinism, myxoedema, and cachexia strumipriva were all due to loss of thyroid function. This was later proved to be true, in 1884, by Horsley's production of myxoedema in monkeys by thyroidectomy.
39. Schiff, Moritz. 1823-1896.  
Résumé d'une nouvelle série d'expériences sur les effets de l'ablation des corps thyroïdes.  
In: *Revue médicale de la Suisse romande*, Genève, 1884, vol. 4, opened at p. 436.  
The author showed that the fatal results which followed his operations, reported in 1859, could be obviated by the previous transplantation of thyroid. His work was done on animals.
40. Horsley, (Sir) Victor. 1857-1916.  
The Brown lectures on pathology.  
In: *Brit. med. jour.*, London, Jan. 17, 1885, opened at p. 111.  
The author supported Felix Semon's hypothesis that myxoedema, cretinism, and cachexia strumipriva were all phases of the one condition and all due to thyroid deficiency. Horsley artificially produced myxoedema in monkeys by thyroidectomy.
41. Bettencourt, R. & Serrano, J. A.  
[Un cas de myxoedème traité par la greffe hypodermique du corps thyroïde du mouton].  
In: *Progrès médical*, Paris, 2. sér., 1890, vol. 12, opened at p. 170.  
They appear to be the first to attempt transplantation of thyroid in a myx-

- oedematous patient. Striking improvement followed, but they do not report permanent relief of symptoms.
42. Horsley, (Sir) Victor. 1857-1916.  
Note on a possible means of arresting the progress of myxoedema, cachexia strumipriva, and allied diseases.  
In: *Brit. med. jour.*, London, Feb. 8, 1890, opened at p. 287.  
The author suggested that myxoedema and other forms of thyroid deficiency in human beings might be successfully treated by the implantation of thyroid tissue in the patient. He suggests using the gland of a sheep. He does not appear to have tried it, however. In 1884, Schiff had showed that the fatal results of thyroidectomies in dogs could be avoided by the transplantation of the gland.
43. Murray, George Redmayne. 1865-1939.  
Note on the treatment of myxoedema by hypodermic injections of an extract of the thyroid gland of a sheep.  
In: *Brit. med. jour.*, London, Oct. 10, 1891, opened at p. 796.  
He was the first to use a subcutaneous injection of thyroid extract in the treatment of myxoedema in human beings. The results were highly successful. The complete life history of this patient is given in the *Brit. med. jour.*, March 13, 1920.
44. MacKenzie, Hector W. G.  
A case of myxoedema treated with great benefit by feeding with fresh thyroid glands.  
In: *Brit. med. jour.*, London, Oct. 29, 1892, opened at p. 940.
45. Fox, E. L.  
A case of myxoedema treated by taking extract of thyroid by the mouth.  
In: *Brit. med. jour.*, London, Oct. 29, 1892, opened at p. 941.  
Following Murray's remarkable success (1891) with subcutaneous injection of thyroid extract, MacKenzie and Fox, independently, showed that equally successful results could be obtained from oral administration of the gland. Both reported toxic symptoms when the dosage was too large.
46. Magnus-Levy, Adolf.  
Ueber den respiratorischen gaswechsel unter dem einfluss der thyreoidea sowie unter verschiedenen pathologische zuständen.  
In: *Berlin. klin. woch.*, July 29, 1895, opened at p. 650.  
The author introduced the experimental method of determining thyroid disturbances. He confirmed the observations of Müller (1893) on the effects of thyroid disorders on the metabolic rate. The investigations of Magnus-Levy laid the foundation for the modern conception of thyroid function: maintenance of metabolism at its proper level through the secretion of an adequate amount of the hormone.
47. Baumann, Eugen.  
Ueber das normale vorkommen von jod im thierkörper.  
In: *Hoppe-Seyler's zeitschrift für physiologische chemie*, Strassburg, 1895/96, vol. 21, opened at p. [319].  
The first good paper on the chemical knowledge of the thyroid. The author proved that the normal gland contains iodine, by isolating an iodine-containing compound to which he gave the name "Thyrojodin". He considered this substance to be closely related to the physiological activity of the gland.
48. Kendall, Edward Calvin. 1886-  
The isolation in crystalline form of the compound containing iodine which occurs in the thyroid; its chemical nature and physiological activity.  
In: *Trans. Assoc. Amer. phys.*, Phil., 1915, vol. 30, opened at p. [420].  
A great contribution to physiology and therapy was made by the author in 1914, by the isolation, in crystalline form, of the iodine-containing hormone of the thyroid, called thyroxin.
49. Marine, David (1880- ) & Kimball, O. P.  
The prevention of simple goiter in man.  
In: *Jour. lab. and clin. med.*, St. Louis, Mo., 1917, vol. 3, opened at p. 40.  
They show how to eradicate simple goiter in regions where the water and soil are deficient in iodine. This was achieved by the oral administration of iodine.

50. Halsted, William Stewart. 1852-1922.  
The operative story of goiter. The author's operation.  
In: *Johns Hopkins hospital reports*, Balt., 1920, vol. 19, opened at p. 193.  
Halsted was considered one of the masters in the art of thyroidectomy, ranking second only to Kocher. On p. 193 begins the account of his own technique which gained for him the reputation of being unexcelled in the field.
51. Harington, Charles Robert. 1897-  
Isolation of thyroxine from the thyroid gland.  
In: *Biochem. jour.*, Cambridge, [Eng.], 1926, vol. 20, opened at p. [293].  
The author gives the "probable empirical formula of thyroxine" as  $C_{15}H_{11}O_4N_4$ .
52. Harington, Charles Robert (1897- ) & Barger, George. (1878- )  
Constitution and synthesis of thyroxine.  
In: *Biochem. jour.*, Cambridge [Eng.], 1927, vol. 21, opened at p. 169.  
The authors verify the chemical formula put forth by Harington in 1926, and describe the synthesis of thyroxine.
53. Sayers, Dorothy Leigh. 1893-  
The incredible elopement of Lord Peter Wimsey.  
In her: *Hangman's holiday*, New York, 1933, opened at p. [41].  
The thyroid gland in fiction. The plot centers around a case of hypothyroidism.

#### THE THYROID AND ITS HYPERFUNCTION: EXOPHTHALMIC GOITER

54. Parry, Caleb Hillier. 1755-1822.  
Enlargement of the thyroid gland in connection with enlargement or palpitation of the heart.  
In his: *Collections from the unpublished medical writings* . . . London, 1825, vol. 2, opened at p. [111].  
The author was the first to describe the disease we now know as exophthalmic goiter. As early as 1786 he recognized disturbances of cardiac function in hyperthyroidism, thus preceding by many years the observations of Flajani, Graves and von Basedow. Osler said that if any person's name were given to the disease it should be that of Parry.
55. Flajani, Giuseppe. 1741-1808.  
Sopra un tumor freddo nell' anterior parte del collo detto broncocele.  
In his: *Collezione d'osservazioni e riflessioni di chirurgia*, Roma, 1802, vol. 3, opened at p. 270.  
The author described cardiac disturbances in thyroid enlargement. His account is considered one of the earliest of exophthalmic goiter, though it has also been said that it is hard to be certain he was actually describing this disease.  
Borrowed through the kindness of the Army Medical Library.
56. Graves, Robert James. 1797-1853.  
Clinical lectures. Lecture XII . . . Newly observed affection of the thyroid gland in females.  
In: *London med. & surg. jour.* (Renshaw ed.), 1835, vol. 7, opened at p. 516.  
The author described the syndrome of hyperthyroidism or exophthalmic goiter—the disease which bears his name. Like Parry, who preceded him, Graves was impressed by the cardiac disturbances associated with this condition. Graves, however, considered the alterations in cardiac function not to be organic in nature. He also concluded that the hypertrophy of the thyroid differed essentially from that in ordinary goiter. Borrowed through the kindness of the Boston Medical Library.
57. von Basedow, Carl Adolph. 1799-1854.  
Exophthalmos durch hypertrophie des zellgewebes in der augenhöhle.  
In: *Wochenschr. f. d. ges. heilk.*, Berlin, 1840, opened at p. [197].  
Basedow's classic paper in which he described the "Merseburg Triad" (named from the place in Germany where he lived): enlargement of the thyroid, protrusion of the eyeballs, and rapid heart. Though he was preceded by Parry (1786) and Graves (1835),

- his description of exophthalmic goiter is undoubtedly the clearest. The only symptom lacking in Basedow's clinical picture of the disease as it is now known is the tremor. On p. 200 he mentions having used iodine in a case, some years earlier, with some success. This is probably the first use of iodine in exophthalmic goiter.
58. von Graefe, Albrecht. 1828-1870.  
Ueber Basedow'sche krankheit.  
In: *Deutsche klinik*, Berlin, 1864, vol. 16, opened at p. 158.  
The author described a very important sign in exophthalmic goiter—lagging of the upped lid in looking downward. It is known as "Graefe's sign."
59. Trousseau Armand. 1801-1867.  
Lectures on clinical medicine delivered at the Hôtel-Dieu, Paris.  
London, 1868, opened at p. 587.  
The classic accident in which Trousseau, by mistake, wrote a prescription for tincture of iodine instead of tincture of digitalis, in a case of exophthalmic goiter. The patient improved, but upon discovery of the error, digitalis was substituted for iodine, whereupon the cardiac condition became worse. Iodine therapy was considered unfavorably at the time and Trousseau, in spite of what he called this "exceptional" case, warned against its general use.
60. Cheadle, Walter Butler. 1836-1910.  
Exophthalmic goitre.  
In: *St. George's hospital reports*, London, 1869, vol. 4, opened at p. [175].  
At a time when iodine was considered a dangerous drug in the treatment of exophthalmic goiter, Cheadle reported beneficial results from its use. He recommended the general use of iodine therapy for this condition, but it was not until the twentieth century that it was again restored to favor.
61. Marie, Pierre.  
Sur la nature et sur quelques-uns des symptômes de la maladie de Basedow.  
In: *Arch. d. neural.*, Paris, 1883, vol. 6, opened at p. 79.  
The author added tremor as the fourth cardinal sign in exophthalmic goiter. The previous three were brought out by Basedow in 1840.
62. Rehn, Louis.  
Ueber die exstirpation des kropfs bei morbus Basedowii.  
In: *Berliner klin. woch.*, 1881, vol. 21, opened at p. 163.  
The first thyroidectomy for exophthalmic goiter. The operation was performed in 1880, and in 1883 the patient was presented before the Medical society of Frankfurt.
63. Greenfield, William Smith.  
Some diseases of the thyroid gland.  
In: *Lancet*, London, Dec. 16, 1893, opened at p. 1493.  
The author was the first to describe the pathological anatomy of the thyroid in exophthalmic goiter.
64. Müller, Friedrich.  
Beiträge zur kenntnis der Basedow'schen krankheit.  
In: *Deut. arch. f. klin. med.*, Leipzig, 1893, vol. 51, opened at p. [335].  
The author showed that an increased metabolism accompanies exophthalmic goiter. This was confirmed by Magnus-Levy in 1895, and may be said to have led to the measurement of metabolism as an important index of the physiological condition of the thyroid.
65. Cannon, Walter Bradford (1871- ); Binger, C. A. L. & Fitz, R.  
Experimental hyperthyroidism.  
In: *Amer. jour. of physiol.*, Balt., 1915, vol. 36, opened at p. 363.  
Probably the first successful attempt to produce exophthalmic goiter experimentally. The results give some support to the view that the sympathetic nervous system plays an important rôle in this disease.
66. Plummer, Henry Stanley. 1874-  
Results of administering iodine to patients having exophthalmic goiter.  
In: *Jour. Amer. med. assoc.*, Chic., June 30, 1923, opened at p. 1955.  
A recommendation for the pre-operative treatment of exophthalmic goiter with iodine. This was contrary to the existing method of treatment in which iodine was discouraged through fear of "Iod-Basedow." This is the preliminary report of Plummer's successful work. A more extensive report was made by Plummer & Boothby in *Coll. papers Mayo clinic*, 15:565-576, 1923.



## PARATHYROID GLANDS

67. Remak, Robert. 1815-1865.  
Untersuchungen über die entwicklung der wirbelthiere.  
Berlin, 1855, opened at p. 191.  
Sandström thought the following lines showed Remak had seen the parathyroids:  
"Vor kurzem fand ich bei der untersuchung der thymus neugeborener katzen an der oberen spitze der thymus, woselbst in anderen fällen auch wimperblasen vorkommen, eine kleine gelbliche drüse, welche weder mit der thymus, noch mit lymphdrüsen, noch mit der schilddrüse in ihrem bau übereinkommt . . ."
68. Owen, (Sir) Richard. 1804-1892.  
On the anatomy of the Indian rhinoceros . . .  
In: *Transactions of the Zoological society of London*, 1862, vol. 4, opened at p. 48.  
The author appears to have observed the parathyroid glands of the rhinoceros as early as 1850. After describing the thyroid gland he says, "a small compact yellow glandular body was attached to the thyroid at the point where the veins emerge."  
Borrowed through the kindness of the American Museum of Natural History.
69. Virchow, Rudolf Ludwig Karl. 1821-1902.  
Die krankhaften geschwülste . . .  
Berlin, 1863-67, vol. 3, pt. 1, opened at p. 13.  
Virchow, too, indicates that he has seen the parathyroid glands.
70. Sandström, Ivar Victor. 1852-1889.  
Om en ny körtel hos menniskan och atskilliga däggdjur.  
In: *Upsala läkareförenings förhandlingar*, 1879/80, vol. 15, opened at p. [441].  
The author is credited with the discovery of the parathyroid glands which he named "Glandulae parathyreoidae," and which he first observed in a dog in 1877. He thought that statements by Remak and Virchow indicated that these men had seen the glands. The only entire translation of this paper is in English by Dr. Carl M. Seipel and appeared in *Bull. Inst. hist. med.*, 6:192-222, 1938.
71. Gley, Eugene.  
Note sur les fonctions de la glande thyroïde chez le lapin et chez le chien.  
In: *Compt. rend. hebdomad. Soc. de biol.*, Paris, 9. sér., 1891, vol. 3, opened at p. 843.
72. Gley, Eugene & Nicolas, A.  
Premiers résultats de recherches sur les modifications histologiques des glandules thyroïdiennes après la thyroïdectomie.  
In: *Compt. rend. hebdomad. Soc. de biol.*, Paris, 10. sér., 1895, vol. 2, opened at p. 216.
73. Vassale, G. & Generali, F.  
Sugli effetti dell' estirpazione delle ghiandole paratiroidee.  
In: *Riv. di pat. nerv. e ment.*, Firenze, 1896, vol. 1, opened at p. 95.  
Three important contributions to the physiology of the parathyroid glands. They explained the fatal results following complete thyroidectomies in which the parathyroids were also removed.
74. Welsh, David Arthur.  
Concerning the parathyroid glands: a critical, anatomical, and experimental study.  
In: *Jour. of anat. and physiol.* . . . London, 1898, vol. 32, opened at p. [292].  
The first contribution to the histology of the parathyroids.
75. Benjamins, C. E.  
Ueber die glandulae parathyreoidae (epithelkörperchen).  
In: *Beitr. z. pathol. anat.* . . . Jena, 1902, vol. 31, opened at p. [143].  
An early reference to parathyroid tumors, but with no reference to bone conditions.
76. Jeandelize, P.  
Insuffisance thyroïdienne et parathyroïdienne; étude expérimentale et clinique.  
In: *Revue neurologique*, Paris, 1903, vol. 11, opened at p. 258.  
He was the first to suggest that epilepsy, tetany and convulsions of child-

hood may be due to parathyroid deficiency.

77. Lundborg, Herman.

Spielein die glandulac parathyreoideac in der menschlichen pathologie eine rolle?

In: *Deut. zeitschr. f. nervenheilk.*, Leipzig, 1904, vol. 27, opened at p. [217].

The author suggested a relationship between the parathyroids and the physiology of the muscles and nerves.

78. Halsted, William Stewart. 1852-1922.

Hypoparathyreosis, status parathyreoprivus, and transplantation of the parathyroid glands.

In: *Amer. jour. med. sci.*, Phil. & N. Y., new ser., 1907, vol. 134, opened at p. [1].

One of the author's contributions to the study of the parathyroid glands. He discusses experiments on the transplantation of the glands.

79. MacCallum, William George (1874- ) & Voegtlin, Carl. (1879- ).

On the relation of the parathyroids to

calcium metabolism and the nature of tetany.

In: *Johns Hopkins hosp. bull.*, Balt., 1908, vol. 19, opened at p. 91.

These authors were the first to demonstrate that the function of the parathyroid glands is to regulate the calcium metabolism of the body. This is a preliminary report.

80. Hanson, Adolph Melanchton. 1888-

An elementary chemical study of the parathyroid glands of cattle.

In: *Military surgeon*, Wash., D. C., 1923, vol. 52, opened at p. 280.

The first of the author's papers on the isolation of the active principle of the parathyroid glands.

81. Collip, James Bertram. 1892-

The extraction of a parathyroid hormone which will prevent or control parathyroid tetany and which regulates the level of blood calcium.

In: *Jour. biol. chem.*, Balt., 1925, vol. 63, opened at p. [395].

The author's isolation of the parathyroid hormone.

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*Classic descriptions of disease* (Major). 2. ed., Springfield, Ill. & Balt., 1939.

Copenhaver, N. H. Peaks and pioneers in the history of the thyroid. In: *Rhode Island M. J.*, 21:180-182, 1938.

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FRANK PLACE

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### DEATHS OF FELLOWS

HAWKES, FORBES: 124 East 65 Street, New York; born in New York, August 25, 1865; died August 24, 1940; graduated in medicine from the College of Physicians and Surgeons, New York, in 1891; elected a Fellow of the Academy November 7, 1895.

Dr. Hawkes was a member of the State and County Medical Societies and of the American Medical Association, a Fellow of the American College of Surgeons, a member of the New York Surgical Society and of the Society of Alumni of Presbyterian Hospital. He was Consulting Surgeon to the Presbyterian, Flower and Fifth Avenue, Nassau and Flushing Hospitals and to the Northwestern Dispensary.

HAYS, HAROLD M.: 136 East 57 Street, New York; born in Rochester, N. Y., September 26, 1880; died in Scarsdale, N. Y., August 20, 1940; graduated in medicine from the College of Physicians and Surgeons, New York, in 1905; elected a Fellow of the Academy May 6, 1909.

Dr. Hays was a member of the State and County Medical Societies, and of the American Medical Association, a Fellow of the American College of Surgeons, a member of the American Academy of Ophthalmology and Otolaryngology and of the American Laryngological, Rhinological and Otolaryngological Society, and of the Alumni of the Mount Sinai Hospital. He was Consulting Otologist to St. Joseph's Hospital at Far Rockaway.

HICKS, HORACE MADISON, 19 Division Street, Amsterdam, N. Y.; born in Delta (Oneida County), New York, November 5, 1862; died in Amsterdam, N. Y., July 19, 1940; graduated in medicine from Chicago Homeopathic Medical College in 1886; elected a fellow of the Academy October 7, 1915.

Dr. Hicks was a member of the State and County Medical Societies and of the American Medical Association. He was Surgeon to the City and St. Mary's Hospitals of Amsterdam, N. Y.

HILL, IRA LEON: 2 East 55 Street, New York; born in Detroit, Michigan, November 6, 1875; died September 2, 1940; graduated in medicine from the Detroit College of Medicine in 1899; elected a Fellow of the Academy April 2, 1903.

Dr. Hill was a member of the State and County Medical Societies and of the American Medical Association. He was also Consulting Obstetrician to the Booth Memorial Hospital and Director and Chief of Staff of the Berwind Maternity Hospital.

KEX, BEN WITT: 100 West 59 Street, New York City; born in Cuthbert, Georgia, June 11, 1883; died in New York City, June 5, 1940; graduated in medicine from the

Medical Department, University of Pennsylvania in 1909; elected a Fellow of the Academy October 7, 1915.

Dr. Key was associate ophthalmologist to the French Hospital, consulting ophthalmologist to the Lutheran Hospital and honorary surgeon to the New York Eye and Ear Infirmary. From 1912 to 1926, Dr. Key was instructor in ophthalmology at the New York University Medical College. He was a diplomate of the American Board of Ophthalmology, a Fellow of the American Medical Association, the American College of Surgeons and a member of the American Ophthalmological Society, the American Academy of Ophthalmology and Otolaryngology and the County and State Medical Societies.

LOTH, MATHILDE: 56 Seventh Avenue, New York; born in New York, April 30, 1896; died August 29, 1940; graduated in medicine from Yale University Medical School in 1922; elected a Fellow of the Academy April 6, 1933.

Dr. Loth was a member of the State and County Medical Societies and of the American Medical Association, and Assistant Pediatrician at the Vanderbilt Clinic and Babies Hospital.

MAGID, MAURICE OLIVER: 1230 Park Avenue, New York City; born in Skalat, Austria, October 24, 1882; died in New York City, July 31, 1940; graduated in medicine from Cornell University Medical College in 1905; elected a Fellow of the Academy May 3, 1923.

Dr. Magid was attending gynecologist to the New York City Correction Hospital and associate gynecologist to the Bronx Hospital. He was a Fellow of the American Medical Association and a member of the County and State Medical Societies.

MARIE, PIERRE: born in Paris, France, September 9, 1853; died near Toulon, France, April 12, 1940; elected an Honorary Fellow of the Academy February 4, 1904.

Professor Pierre Marie became an intern in 1876 and in 1883 he received the degree of Doctor of Medicine for his classic study "Sur les formes frustes de la maladie de Basedow." In 1885 he entered the Salpêtrière

as head of Charcot's clinic. From that period dates the study on progressive muscular atrophy which is known as the Charcot-Marie type. Then followed an appointment as professor of pathological anatomy and head of the Hospice de Bicêtre, where he founded a notable collection of pathological material. In 1907 he was elected to the chair for neurology of the University of Paris, and in 1911 he was elected a member of the Académie de Médecine de Paris.

The works which first called the attention of the medical world to Professor Marie were his studies on acromegaly (1886), on hypertrophic pulmonary osteo-arthritis (1890), and spondylosis rhizomelica (1898). His greatest claim to fame arises from his outstanding original work in the field of neurology. The contribution to medicine which carried his name far beyond the confines of the medical profession was a group of four papers on the localization of aphasia (1906-07). It upset a number of universally accepted dogmas and established an entirely new doctrine of cerebral localizations and the function of speech.

Professor Marie was a charter member and first general secretary of the Société de Neurologie and together with Brissaud he founded the *Revue Neurologique*.

MCBARRON, JOHN DUFF: 634 West End Avenue, New York; born in New York, June 8, 1867; died in New York, August 25, 1940; graduated in medicine from the College of Physicians and Surgeons, New York, in 1892; elected a Fellow of the Academy February 5, 1903.

Dr. McBarron was a member of the State and County Medical Societies and of the American Medical Association.

MORTON, HENRY HOLBICH: 32 Schermerhorn Street, Brooklyn, New York; born in Hoboken, New Jersey, June 17, 1861; died in Gulfport, Florida, May 3, 1940; graduated in medicine from the Long Island College Hospital in 1882; elected a Fellow of the Academy January 7, 1897.

Dr. Morton was emeritus professor of urology at the Long Island College and consulting urologist to the Kings County, Long Island College, Flushing, Sea View, Bushwick and St. Peter's Hospitals. He was

a diplomate of the American Board of Urology, a Fellow of the American College of Surgeons and the American Medical Association, a member of the American Association of Genito-Urinary Surgeons, the American Urological Association, and the Kings County and New York State Medical Societies.

Dr. Morton was a contributor to medical journals and was the author of "Genito-Urinary Diseases and Syphilis."

PARKER, RANSOM JOSEPH: 2 East 54 Street, New York City; born in Chicago, Illinois, March 8, 1870; died in New York City, May 4, 1940; graduated in medicine from the College of Physicians and Surgeons, Columbia University, in 1893; elected a Fellow of the Academy April 5, 1906. He was a Fellow of the American Medical Association and a member of the County and State Medical Societies.

PERLA, DAVID: Montefiore Hospital, Bronx, New York; born in New York City, July 13, 1900; died in New York City, June 14, 1940; received the degree of B.S. from Columbia University in 1921 and graduated in medicine from the College of Physicians and Surgeons, Columbia University, in 1923; elected a Fellow of the Academy January 3, 1930.

Dr. Perla was instructor in medicine at the College of Physicians and Surgeons, Columbia University, and associate pathologist and immunologist to the Montefiore Hospital. He was a diplomate of the American Board of Pathology, a member of the American Association of Pathologists and Bacteriologists, the American Association of Immunologists, the American Society for Experimental Pathology, the New York Pathological Society, the American Medical Association and the County and State Medical Societies.

SEYMOUR, NAN GILBERT: 134 East 19 Street, New York City; born in Peekskill, New York, August 4, 1875; died in New York City, May 27, 1940; graduated in medicine from Cornell University Medical College in 1902; elected a Fellow of the Academy January 3, 1924.

Dr. Seymour was medical director since its founding in 1905 of the William Booth

Memorial Hospital, a Fellow of the American Medical Association and a member of the County and State Medical Societies.

SPILLER, WILLIAM GIBSON: 3400 Spruce Street, Philadelphia, Pennsylvania; born in Baltimore, Maryland, September 13, 1863; died in Philadelphia, March 19, 1940; received from the University of Pennsylvania the degree of M.D. in 1892, Sc.D. in 1934, and from Lafayette College LL.D. in 1934; elected an Honorary Fellow of the Academy March 2, 1933.

Dr. Spiller was emeritus professor of neurology at both the medical school and graduate school of medicine of the University of Pennsylvania, having served that institution as assistant clinical professor of nervous diseases and assistant professor of neuropathology, 1901-03; professor of neuropathology and associate professor of neurology, 1903-15; and professor of neurology, 1915-32. From 1902-25 he had served also as clinical professor at the Woman's Medical College of Pennsylvania. He was honorary consulting neurologist to the Philadelphia General Hospital and at one time professor of nervous diseases at the Philadelphia Polyclinic Hospital.

Dr. Spiller was a member of the American Neurological Association and its president in 1915, a Fellow of the American Medical Association, a Fellow of the American College of Physicians, a corresponding member of the Gesellschaft deutscher Nervenärzte, Société de Neurologie de Paris, Verein für Psychiatrie und Neurologie (Vienna); and an Honorary Member of the Société Esthonienne de Neurologie.

WALDO, RALPH, Westhampton, N. Y.; born in Scotland (Windham County), Connecticut, September 24, 1860; died in Hollis, Queens, August 6, 1940; graduated in medicine from the Medical Department of New York University in 1882; elected a Fellow of the Academy February 7, 1889.

Dr. Waldo was chief surgeon to the Lebanon Hospital and he also founded the nursing school there. He had been consulting gynecologist to the Rockaway Beach, Nyack and Southampton Hospitals and also was on the staff of the Post-Graduate and Woman's Hospitals.

## PHYSICIANS NEEDED FOR ARMY SERVICE

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The physician, like every other American, has become actively interested in our national security and stands ready to contribute his services as required for military preparedness.

The immediate problem in this connection is one that concerns the War Department, and primarily the young physician. The War Department must procure sufficient additional personnel from the medical profession to augment the medical services of the Regular Army as the various increases are made in the strength of the Regular Army, as authorized by Congress to meet the partial emergency. The young physician is especially concerned because it is usually advantageous, and is often more convenient for him to serve with the Army.

Present plans of the War Department are designed to make service attractive and instructive for the young physician. If the physician holds a Medical Corps Reserve commission he can be ordered to active duty if he so requests. If he does not hold a commission, but is under 35 years of age and is a comparatively recent graduate of an accredited school, he may secure an appointment in the Medical Corps Reserve for the purpose of obtaining extended active duty for a period of one year or longer. Duty is given at General Hospitals, Station Hospitals, and with Tactical Units, and embraces all fields of general and specialized medicine and surgery. Excellent post-graduate training is obtainable in connection with Aviation Medicine. After serving 6 months of active duty in the continental United States, a Reserve officer may request duty in Hawaii, Panama, or other United States territories and possessions. The initial period for duty is for one year and yearly extensions are obtainable thereafter until the international situation becomes more clarified and our domestic military program becomes stabilized.

Many young doctors who have served with the Army on extended active duty have taken the competitive examination for entrance into the Medical Corps of the Regular Army. Extended active duty affords an excellent opportunity for the physician to observe modern military medicine and the facilities that exist for a complete and comprehensive medical practice.

Further information may be obtained by writing to The Surgeon General, U. S. Army, Washington, D. C.

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OF MEDICINE



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EXPERIMENTAL BASIS OF CHEMOTHERAPY  
IN THE TREATMENT OF BACTERIAL  
INFECTIONS\*

*The Ludwig Kast Lecture*

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Department of Pharmacology and Experimental Therapeutics, The Johns Hopkins University

THE use of sulfonamide drugs in the treatment of bacterial infections is based upon studies involving the effect of the drugs upon experimental infections in animals, the effect of the drugs upon various bacteria *in vitro*, and the effect of the drugs upon the host organism. This last includes a determination of the acute and chronic toxicity of a drug for several species of animals, its action on individual organs and tissues, its absorption, excretion and distribution, and the changes undergone by the drug in passing through the host. In all of these studies, it has been of the greatest value to have available accurate and simple methods for determining drug concentrations in blood, urine, body fluids and tissues.<sup>1, 2, 3, 4, 5</sup> These methods, I think, have been responsible more than anything else for placing the schedule of dosage of bacterial chemotherapeutic agents on a rational basis.

Nearly all research directed toward the chemotherapy of experi-

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\* Read October 14, 1940 in the Graduate Fortnight of The New York Academy of Medicine.



mental bacterial infections has utilized the mouse as the experimental animal. In the original observations of Domagk<sup>6</sup> on Prontosil, the discovery of the antibacterial activity of sulfanilamide,<sup>7</sup> the observations of Colebrook and Kenny,<sup>8</sup> Buttle, Gray and Stephenson<sup>9</sup> and Long and Bliss<sup>10</sup> on experimental streptococcus infections, and the study of the activity of sulfapyridine in pneumococcus infection,<sup>11</sup> all utilized the mouse to furnish the basis for the clinical trial of these three drugs. In the above cases, the transfer of results from the lowly mouse to man has been justified by subsequent clinical experience, but this will probably not always be so.

Relatively simple methods of treating infected mice suffice for detecting the antibacterial activity of a drug against the particular organism used, but a more elaborate procedure is necessary to evaluate such activity quantitatively. In the early studies of the influence of sulfanilamide on pneumococcus infections in mice, there is agreement of opinion that the drug possessed some activity; however, most observers reported that although death could be delayed in treated mice, recovery from the infection did not occur. The impression gained from these studies was that sulfanilamide had slight therapeutic value against the pneumococcus and apparently this prevented its thorough trial in pneumonia. Recently, in a careful study of mouse infection with forty-seven strains of the thirty types of pneumococci, Schmidt and Hilles<sup>12</sup> found that the therapeutic effectiveness of sulfanilamide was considerable; in some cases 100 per cent survivals resulted. They administered the drug every 6 hours, day and night, maintaining a blood concentration of 8 to 12 mgm. per cent, and showed that the infrequent administration of the drug was responsible for the failure of earlier observers to obtain beneficial effects. We have little data on the clinical value of sulfanilamide in pneumonia because sulfapyridine has already established itself. However, in the one careful study of its use, very good results are reported.<sup>13</sup>

In order to use *in vivo* studies of the sulfonamide derivatives against various bacteria in the mouse to point the way to the selection of the most effective drugs for clinical trial, it is necessary to have an accurate quantitative method for the evaluation of the effectiveness of various compounds. Data on the effectiveness of drugs in infected mice have usually been obtained by administration of doses of the drugs according to schedules which have differed with each investi-

gator. Marked variation in blood concentrations of drug must have resulted from the different dosage schedules employed as well as from differences in the absorption, excretion and distribution of the various drugs. Another difficulty has been the lack of a suitable therapeutic response for an end-point. Recently, we have developed in our laboratory a method for the quantitative evaluation of chemotherapeutic agents in bacterial infections in mice which appears to give a more or less absolute comparison of two drugs independent of many variables within the experiment.<sup>14, 15, 16</sup> The method need not be described as it is given in detail in the communications to which reference is made. The quantitative data for several drugs in a streptococcus and a pneumococcus infection in mice appear to indicate some specificity on the part of these drugs for different bacterial infections.

Numerous *in vitro* studies of the effect of various sulfonamide drugs have been reported against bacteria. These have had two purposes, an elucidation of the mode of action, and an appraisal of the drug for clinical use. However, the concentration of a drug necessary to produce a bacteriostatic or bactericidal action *in vitro* may have absolutely no apparent relation to that necessary for its *in vivo* activity. Concentrations of sulfanilamide of 10 to 20 mgm. per cent may result, in experiments *in vitro* on streptococci, in no effect, in bacteriostasis or in bactericidal effects, while much lower blood concentrations are effective in the treatment of streptococcus peritonitis in mice. We know now that the strain of streptococcus, the size of the initial inoculum, the composition of the medium (particularly the amount of antisulfanilamide factor present), and the temperature at which the test is performed have a marked effect on the result obtained.<sup>17, 18</sup> The question arises as to whether the comparative activity of different drugs *in vitro* may not give information concerning their relative activity *in vivo* on the same organism. Unfortunately, little quantitative information is available to answer this query. Sulfapyridine is about two or three times as active as sulfanilamide *in vitro*, but the two drugs show equal activity *in vivo* in the mouse against the same strain of streptococcus. Diaminodiphenylsulfone and sulfathiazole show many times the activity of sulfanilamide *in vitro*, but the former is only three times as active and the latter is no more active than sulfanilamide *in vivo* in the mouse.<sup>15</sup> It is probable that high bacteriostatic or bactericidal activity *in vitro* is only one of the prerequisites for high *in vivo* activity. For systemic infections, it appears

that *in vivo* studies in the mouse are more valuable than *in vitro* studies in pointing the way to the selection of the most effective drugs for clinical trial.

In the treatment of urinary tract infections and infections confined to the intestine, as well as in the local use of these drugs in infected wounds, the comparative *in vitro* activity of different sulfonamide drugs may be valuable as an aid for selecting drugs for clinical trial, as body defences may well play a minor role under these conditions. The greater *in vitro* activity of sulfapyridine<sup>19</sup> and sulfathiazole<sup>20,21</sup> on bacteria found in urinary infections suggests that, other things being equal, these two drugs would be superior to sulfanilamide in treating urinary infections. Recently, in the course of a study of sulfanilylguanidine as a possible intestinal chemotherapeutic agent, we<sup>22</sup> found that this drug caused a marked reduction of the coliform organisms in the stools of mice fed the drug in their diet. It seems probable that pathogenic organisms in the intestinal tract which are more susceptible to sulfanilylguanidine *in vitro* than *E. coli* will likewise be more susceptible in the intestinal tract. In the case of such diseases as subacute bacterial endocarditis caused by *Streptococcus viridans*, with which one cannot produce satisfactory infections in experimental animals, one must rely upon the unsatisfactory *in vitro* studies of the activity of drugs.

It is obvious, however, that other factors besides comparative chemotherapeutic activity in mice and bacteriostatic or bactericidal activity *in vitro* must of necessity govern the selection of the most suitable drug for clinical trial in man. Such factors are contained in a study of the drug on the host. An assessment of the probable toxicity of a drug in the human being is of prime importance. In the first communication on the pharmacology of sulfapyridine,<sup>23</sup> this drug was stated to be about one-fourth as toxic as sulfanilamide. However, the poor absorption of sulfapyridine from the gastrointestinal tract prevents a determination of its true toxicity when the drug is given *per os*. By the use of a soluble sodium salt of sulfapyridine it has been shown that on the basis of blood concentration, this drug is more toxic acutely for mice, rabbits, and dogs than is sulfanilamide.<sup>24</sup> No information is available as to the chronic toxicity of sulfapyridine based on a maintained and known blood concentration of the drug. However, studies have been made of the effect of the repeated administration of one dose per day by

mouth:<sup>25, 26</sup> these have shown no toxicity except that resulting from the deposition of acetylsulfapyridine in the form of concretions and stones in the urinary tract of rats,<sup>27</sup> rabbits and monkeys. It is interesting to note that clinically sulfapyridine appears to be considerably more toxic than sulfanilamide.<sup>28</sup>

Sulfathiazole is less toxic acutely than sulfapyridine for mice<sup>29, 30</sup> and dogs; its chronic toxicity for mice<sup>29</sup> and rabbits appears to be greater and for rats and monkeys<sup>29</sup> less than that of sulfapyridine. However, the study of chronic toxicity of these drugs is complicated by the formation of acetyl-derivatives which may cause mechanical damage to tissues.

The above examples of determination of toxicity on animals illustrate how difficult it is to transfer such data to the human subject. However, if careful studies of chronic toxicity be made in several species of animals with known and maintained blood concentrations of free and conjugated drug, with careful pathological examination of tissues at the end of the experiment, and especially if attempts are made to determine the kind of toxicity which does not kill the animals—effects on blood, cerebral cortex, vomiting center, spinal cord, peripheral nerves, liver, kidneys, etc.—it would appear possible to make fairly accurate prediction for the human subject. In the above discussion of the toxicity of these drugs, evidence of toxicity has been usually based upon death of the animals, symptoms of toxicity observable with the naked eye, and upon pathological changes in the tissues. However, evidence is available that one drug may be more toxic than another to one system of the body, while the reverse may be true with another system. For example, sulfapyridine is about twice as toxic acutely as sulfanilamide on the basis of the death of mice,<sup>24</sup> yet sulfapyridine is only one-half as toxic to the hematopoietic system as sulfanilamide.<sup>31</sup> The use of the so-called chemotherapeutic index, which expresses the ratio between the dosage producing death and the dosage producing a therapeutic response, is of little value, and can be extremely misleading. Of course, it is at present impossible to predict hypersensitiveness and idiosyncrasy that may result from the drug in man. Determinations of the toxicity on animals should be comparative; sulfanilamide or sulfapyridine, the human toxicity of which is fairly well known, can be used as standards.

It is necessary to have information concerning the absorption, excretion, and distribution of these drugs before they can be used most effi-

ciently in the treatment of disease. It now seems proven that the maintenance of a certain concentration of drug in blood and tissues for several days is most efficient for treating infections. To accomplish this the dosage of a drug must be properly spaced, but to do this data concerning its absorption and excretion are necessary. With sulfanilamide, absorption from the gastrointestinal tract is complete and a peak blood concentration is reached in 3 to 5 hours;<sup>2</sup> therefore, it is rational to space doses at 4-hour intervals. Rapidity of excretion may necessitate frequent dosage, but a high rate of excretion is of great advantage for freeing the body of the drug when administration has to be stopped on account of toxic manifestations. Rapid excretion is a great advantage in the case of a drug to be used as a urinary antiseptic; a lower blood level of such a drug will give the same urinary concentration as would be obtained with a higher blood concentration of a less rapidly excreted drug. In the case of sulfanilamide, it has been shown that increasing the rate of urine flow by administration of water increases the rate of elimination of the drug;<sup>32</sup> this is probably also true of sulfapyridine and of sulfathiazole. The rapid diffusibility of a drug to all the tissues and fluids of the body and its presence in them in about the same concentration as in the blood is apparently a valuable asset for a good chemotherapeutic agent. This has been shown to be true for sulfanilamide<sup>33</sup> and for sulfapyridine.<sup>34</sup> No complete data are available for sulfathiazole, but it is known that this drug does not pass into the spinal fluid as rapidly as do sulfanilamide and sulfapyridine.<sup>34</sup> Hence, for treating meningitis sulfathiazole is not suitable to replace either sulfanilamide or sulfapyridine.

In conclusion, a brief discussion of the individual variation in the response to these drugs may be given. One finds in clinical reports on the therapeutic efficiency of these drugs statements expressing surprise that no correlation appears to exist between the blood concentration and either the therapeutic response or some symptoms of toxicity such as nausea and vomiting. With the relatively small amount of data available, this is exactly what one would expect from the individual variation of patients and differences in the strains of infecting organisms. Let me illustrate this matter of biological variation by mentioning some experiments on mice.

In Figure 1, the characteristic curve of the acute toxicity of sulfanilamide for mice when given *per os* is shown. One can calculate that

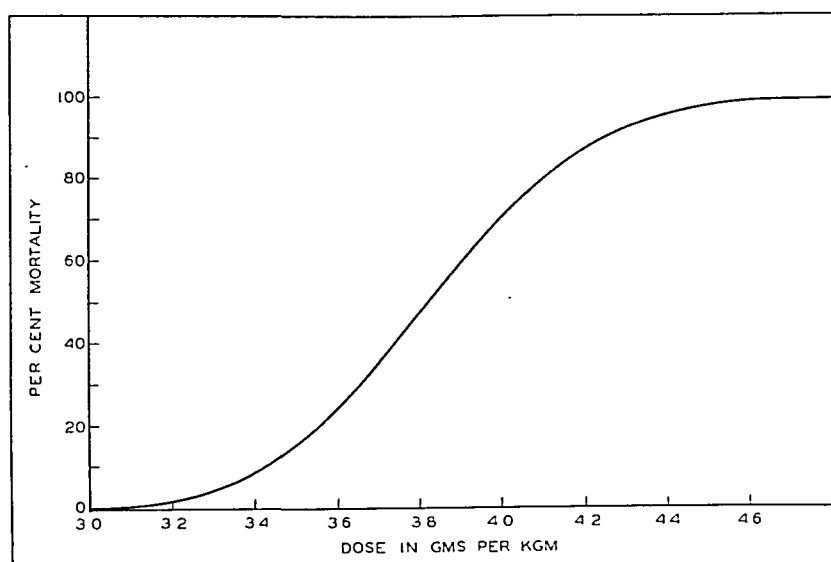


Fig. 1.—Characteristic curve of acute toxicity of sulfanilamide for mice, drawn from data of Marshall and Litchfield.<sup>24</sup>

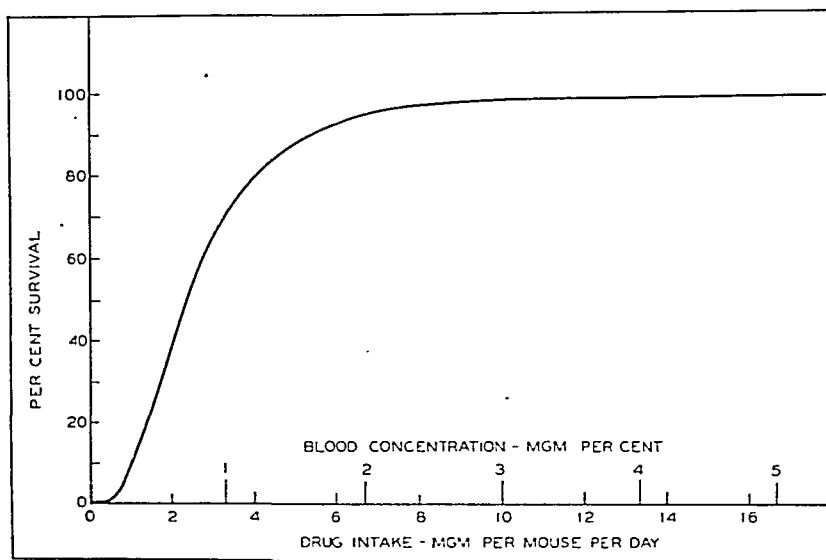


Fig. 2.—Characteristic curve of blood concentration (or drug intake per day) against per cent survival of mice infected with  $\beta$ -hemolytic streptococci and treated with sulfanilamide, redrawn from figure of Marshall, Litchfield and White.<sup>15</sup>

the dose which will kill 1 per cent of the mice is 3.1 gm. per kgm. and that it takes 4.6 gm. per kgm. to kill 99 per cent of the mice. This is not a wide variation. In Figure 2, the characteristic curve of the blood concentration (or drug intake per day) against the percentage survival of mice infected with an invariably rapidly fatal streptococcus infection is shown. While as low a blood concentration as 0.17 mgm. per cent of sulfanilamide maintained for three days will result in a survival of one per cent of the mice, it takes 3.06 mgm. per cent (or 18 times as much) to give a survival of 99 per cent of the mice. This is quite a marked variation. When one considers that sick human beings of widely varying genetic stock infected with different strains or types of an organism are unquestionably much more variable than these mice, it is not surprising but to be expected that in a relatively small series no relation between blood concentration and the toxicity or the therapeutic effect of one of these drugs would be apparent. Also, one would expect that the blood concentration suggested at present for a satisfactory therapeutic response is unnecessarily high for many patients and not high enough for a very few. However, if data from a very large population were analyzed, it is certain that the same continuous variation as seen in mice would be observed.

Let me urge upon the clinicians who are responsible for the treatment of patients with these drugs to try to obtain very accurate data in regard to blood concentration and toxic symptoms or therapeutic effect. If this is done, we shall ultimately be able to analyze such data and possibly improve the treatment of bacterial infections with the sulfonamide group of drugs.

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# THE CLINICAL USE OF SULFANILAMIDE AND ITS DERIVATIVES IN THE TREATMENT AND PROPHYLAXIS OF CERTAIN INFECTIONS\*

*The Wesley M. Carpenter Lecture*

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SINCE the original report by Domagk<sup>1</sup> concerning the chemotherapeutic properties of Prontosil, numerous sulfanilamide derivatives have been introduced for the control of bacterial infections. In many countries these derivatives have been launched with but meager preliminary experimental or clinical data, and with claims of therapeutic potency far beyond the real value of the compounds. Fortunately, in the United States, the advent of sulfanilamide was followed closely by the passage of the present Food and Drug Act, and with the exception of the tragic consequences which resulted from the widespread distribution of "Elixir of Sulfanilamide," all sulfanilamide derivatives which have come into the hands of American physicians, have had a firm background of experimental investigation and clinical application. Out of a welter of drugs, American pharmaceutical manufacturers have wisely pressed claims for only three or four sulfanilamide derivatives, and the Food and Drug Administration and the Council on Pharmacy and Chemistry of the American Medical Association have seen fit to recognize only two of them, namely, sulfathiazole and sulfapyridine. This far-sighted policy on the part of all concerned has limited the list of these chemotherapeutic agents to those of proven merit, and tonight it will be our purpose to attempt to give a clinical evaluation of the use of sulfanilamide, sulfapyridine and sulfathiazole in the prophylaxis and treatment of certain bacterial infections.

Shortly after the introduction of sulfanilamide it became evident, from the work of Marshall and his associates,<sup>2,3</sup> that the rational use of

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drug called for a knowledge of the factors concerning its absorption, distribution, excretion from the body, and the possible toxic effect which it might have. It quickly became evident that successful therapy with sulfanilamide depended upon the maintenance of certain concentrations of the drug in the blood of the patient under treatment. Later, with the introduction of sulfapyridine and sulfathiazole, and with the discovery that they presented different patterns in respect to their passage through the body from those of sulfanilamide, it has become necessary for the physician to possess a sound knowledge of the clinical pharmacology of these compounds if he expects to obtain the greatest measure of therapeutic success from the use of these agents. The problem as to which one of these compounds it is best to employ in a given infection is a real one. Hence, it is imperative when using these compounds to know of their behavior in the body and to have the latest information regarding their comparative effectiveness in disease—types of data which can be based only upon extensive experimental investigations and sound clinical observations.

More is known about the fate of sulfanilamide in the human body than of either of the other two compounds. This drug, when administered by the oral route, is well absorbed from the gastrointestinal tract, is fairly equally distributed throughout the body tissues and, if kidney function is normal, is promptly excreted. The maintenance of adequate concentrations of sulfanilamide requires a dosage schedule that is on a four hour basis. Sulfapyridine is irregularly absorbed by different individuals, and in the same individual the degree of absorption of this drug from the gastrointestinal tract may vary quite markedly from day to day. As far as information is available, the drug is fairly well distributed throughout the tissues, and, as a general rule, it is conjugated to the therapeutically inactive acetyl derivative in a much higher degree than is either sulfanilamide or sulfathiazole. From data available at the present time, it seems that the liver plays the predominant role in the conjugation of sulfanilamide and its derivatives. Sulfapyridine is excreted more slowly than is sulfanilamide or sulfathiazole and in the urine a high percentage of the excreted drug is generally present in the acetylated form. This conjugated fraction is poorly soluble and tends to crystallize out in the urine.

Sulfathiazole is readily absorbed and when kidney function is normal, is rapidly excreted. It is conjugated by the tissues in about the same

degree as has been noted for sulfanilamide. Data which have been obtained from the administration of the drug in patients whose kidney function is depressed and in whom the rate of excretion of the drug is decreased, tend to show that if sulfathiazole remains in the body for any considerable period of time, its rate of conjugation tends to increase rapidly. This suggests that the reason why sulfathiazole does not ordinarily seem to be converted in large amounts to the acetyl form, is that the drug usually is excreted so rapidly that the conjugating mechanism in the liver does not have time to play its ordinary role. The drug is excreted almost entirely by the kidney, and in the urine definitely less sulfathiazole is found in the acetylated form than is the case with sulfapyridine, again, probably, because the drug is excreted so rapidly. This rapid excretion of the drug makes it difficult at times to maintain adequate concentrations of sulfathiazole in the blood. There is little information regarding the distribution of sulfathiazole in the tissues of the body. However, it is known that sulfathiazole passes over much less rapidly into the spinal fluid than does either sulfanilamide or sulfapyridine.

At the present time the sodium salt of sulfapyridine is available for clinical use, and it is probable that the sodium salt of sulfathiazole will be available in the near future. These compounds are made up in 5 per cent solutions in distilled water, *and should always be administered by the intravenous route*. Immediately after these compounds pass into the blood stream, the sodium ion is split off, thus releasing either sulfapyridine or sulfathiazole as the case may be. From this point on, these drugs behave in the tissues in a manner comparable to that noted when they are administered by the peroral route.

In the selection of the drug for the treatment of a given infection, it is of the greatest importance that the correct etiological diagnosis of the disease process be made by bacteriological cultural methods. However, it is our firm opinion that one should never hesitate to employ these chemotherapeutic agents if one feels that, upon the basis of clinical diagnosis, an infection is present which is known to respond to sulfanilamide or its derivatives. The early use of these chemotherapeutic agents in the treatment of susceptible infections is of paramount importance if prompt, clear cut clinical results are to be obtained. Recently, on the basis of experimental and clinical observations, we have attempted to list the drug of choice in the treatment of certain disease processes. We

TABLE I

THE DRUG OF CHOICE IN THE PERORAL TREATMENT OF BACTERIAL INFECTIONS WHICH RESPOND WELL TO CHEMOTHERAPEUTIC AGENTS

Sulfanilamide	Sulfapyridine	Sulfathiazole
Chancroid	Gonococcal Infections	E. coli Tissue Infection
Gas Gangrene	Arthritis	Gonococcal Infections
Cl. Welchii	Endocarditis	Arthritis
Hemolytic Streptococcal Infections	Female Gonorrhea	Male Gonorrhea
Abscesses	Male Gonorrhea	Pneumococcal Infections
Adenitis	Ophthalmia	Pneumonia
Angina (Ludwig's)	Pneumococcal Infections	Staphylococcal Infections
Cellulitis	Mastoiditis	Carbuncle
Empyema	Meningitis	Cellulitis
Erysipelas	Otitis Media	Osteomyelitis
Impetigo	Peritonitis	Pneumonia
Lymphangitis	Pneumonia	Septicemia
Mastoiditis	Sinusitis (Acute)	Urinary Tract Infections
Meningitis	Staphylococcal Infections	A. aerogenes
Miscellaneous	Meningitis	B. pyocyaneus
Osteomyelitis		E. coli
Otitis Media		S. albus
Peritonitis		S. aureus
Peritonsillar Abscess		
Pharyngitis		
Pneumonia		
Puerperal Sepsis		
Scarlet Fever		
Septicemia		
Sinusitis (Acute)		
Tonsillitis		
Ulcers		
Lymphogranuloma		
Venereum		
Meningococcal Infections		
Meningitis		
Septicemia		
Streptococcus Viridans Infections		
Abscesses		
Cellulitis		
Meningitis		
Osteomyelitis		
Periodental Infections		
Septicemia		
Trachoma		
Urinary Tract Infections		
Hemolytic Streptococcal (Group B)		
Proteus		

realize full well that there will be a definite disagreement on the part of some physicians concerning our evaluation of the clinical effectiveness of these drugs.

In Table I are listed the drugs of choice in the peroral treatment of bacterial infections which are known to respond well to therapy with sulfanilamide or its derivatives. There can be little doubt on the basis of present knowledge, that hemolytic streptococcal infections produced by organisms belonging to Lancefield's Group A, are best treated by sulfanilamide. The same seems to hold true for chancroid, Welch bacillus infections (gas gangrene), lymphogranuloma venereum, meningococcal infections, and infections (other than subacute bacterial endocarditis) which are produced by *Streptococcus viridans*, provided that the *Streptococcus viridans* belongs to the mouth group of these organisms and is not an enterococcus. At the present time it seems best that sulfanilamide be used in the therapy of trachoma and urinary tract infections due to the double zone- $\beta$  hemolytic streptococcus (Lancefield's Group B) or to *B. proteus*.

It is to be noted at this point that the use of sulfanilamide in the treatment of gonococcal infections is not recommended. This is based on the observations made by numerous workers during the past two years that sulfapyridine and sulfathiazole are definitely superior to sulfanilamide in the treatment of gonococcal infections. Sulfapyridine, therefore, is an effective agent in the treatment of gonococcal infections, certain pneumococcal infections, and, because it passes readily into the spinal fluid, in staphylococcal meningitis.

There can be little doubt that sulfathiazole is the drug of choice in most staphylococcal infections. As for pneumococcal infections, it seems to be as effective in pneumococcal pneumonia as sulfapyridine, and it produces much less nausea and vomiting in patients. It seems to be as effective in male gonorrhea as is sulfapyridine. From both the experimental and clinical points of view, sulfathiazole appears to be the most effective drug in the treatment of colon bacillary infections of the tissues such as peritonitis, pyelonephritis. In certain urinary tract infections the drug seems to be of considerable value.

In Table II are listed certain diseases in which sulfanilamide or its derivatives have been used, but concerning which not enough reliable data are available to evaluate completely the clinical effects of these drugs. Hence, one cannot recommend these drugs with the utmost con-

TABLE II

DISEASES IN WHICH THE PERORAL ADMINISTRATION OF  
SULFANILAMIDE OR ITS DERIVATIVES HAVE BEEN  
REPORTED TO BE OF SOME VALUE

Sulfanilamide	Sulfapyridine	Sulfathiazole
Actinomycosis	Brucella Infections	Ulcerative Colitis
Brucella Infections	Dermatitis Herpetiformis	
Hemolytic Streptococcal Infections (Lancefield Groups B and C)	Friedländer's Bacillus Infections	
Influenza Bacillus	Pemphigus	
Meningitis	Streptococcus Viridans (Sub-acute Bacterial Endocarditis)	
Lupus Erythematosus	Ulcerative Colitis	
Malaria		
Pemphigus		
Streptococcus Viridans (Sub-acute Bacterial Endocarditis)		
Ulcerative Colitis		

TABLE III

DISEASES IN WHICH SULFANILAMIDE OR ITS DERIVATIVES HAVE  
BEEN USED WITHOUT SATISFACTORILY DEMONSTRATING  
THEIR VALUE

Sulfanilamide	Sulfapyridine	Sulfathiazole
Anaerobic Streptococcal Infections	Anaerobic Streptococcal Infections	Anaerobic Streptococcal Infections
Bacillary Dysentery	Common Colds	Influenza
Common Colds	Influenza	Typhoid
Influenza	Paratyphoid Fever	
Non-Hemolytic Streptococ- cal Infections	Chronic Sinusitis	
Paratyphoid Fever	Tularemia	
Rheumatic Fever (Acute)	Typhoid	
Rocky Mountain Spotted Fever		
Chronic Sinusitis		
Trichomonas Vaginal Infections		
Tuberculosis		
Tularemia		
Typhoid		

fidence that they will accomplish the desired therapeutic results. It is our belief, however, that one should never hesitate at least to try the effects of these drugs in the diseases which have been listed here. The exception to this is malaria in which quinine, Atabrine or Plasmochin are always to be preferred.

In Table III are listed a number of diseases in which sulfanilamide or its derivatives have been tested, and in which there is no good evidence that they have a definite therapeutic value. For this reason their use in these diseases is not advised.

At this point it is important to remember that the rational and reasonable use of these three drugs calls for more thought than just their correct prescription. One must not neglect the patient himself while treating a given infection, and all measures of proven value should be employed when indicated. Of considerable importance is the proper use of surgical procedures when such are advisable. This is especially true in the treatment of the complications of pneumonia, such as empyema, purulent arthritis, the drainage of abscesses occurring in the course of hemolytic streptococcal infections, and especially the incision of purulent foci when sulfathiazole is being prescribed in staphylococcal infections. It has seemed to us that since the introduction of sulfathiazole, possibly a little too much stress has been laid upon the chemotherapeutic activity of this drug in the therapy of staphylococcal infections. On several occasions we have seen individuals suffering from a staphylococcal bacteriemia in whom the administration of the drug brought about a prompt clearing of the blood stream and signs of considerable improvement in the patient. However, in these patients, the temperature and pulse did not come down to normal, and in hopes that further administration of the drug would bring about the desired effect, therapy was kept up over a period of weeks without complete recovery. Finally, sulfathiazole was stopped, and in each instance, hidden and masked foci of infection began slowly to make their appearance. In all instances, multiple surgical procedures were necessary before the patient recovered. These experiences lead us to believe that it is unwise to continue sulfathiazole over periods of weeks in staphylococcal infections, unless there is definite clinical evidence that the patient is constantly improving.

The question of how much fluid should be given to patients who are receiving sulfanilamide or its derivatives is frequently of considerable importance. We have noted repeatedly patients in whom, despite appar-

ently adequate doses of sulfanilamide, it seemed difficult to establish therapeutically active concentrations of sulfanilamide in the blood. In each instance it was found that the patients were receiving such large quantities (4500 cc. to 7000 cc.) of fluids each day that the drug was being excreted almost as rapidly as it was being absorbed. Hence, when patients are receiving sulfanilamide, it is rarely necessary to force fluids beyond 3500 cc. per day.

When sulfapyridine or sulfathiazole is being given to a patient, the administration of adequate amounts of fluids is a prime necessity. This results from the fact that in concentrated urines, the precipitation of acetyl sulfapyridine or acetyl sulfathiazole is more likely to occur and, hence, there is a greater possibility of renal calculi being formed. Therefore, in patients who are receiving either of these drugs, *the urine output should be kept at 1000 cc. or more per day.*

Certain curious beliefs have grown up concerning the diets for patients who are receiving sulfanilamide or its derivatives. Eggs, for instance, are said to be dangerous because of their sulphur content, and because of the possibility that additions of sulphur will facilitate the production of sulphhemoglobin. It is sufficient to say there is not a bit of data available which would lead one to believe that such a superstition has any foundation in fact.

Also, as far as we know, there are no contraindications to the concurrent administration of other necessary drugs, provided that there are definite indications for such prescriptions. The possible exception to this statement is the use of *anesthetic* (not sedative) doses of certain barbiturates in patients receiving sulfanilamide or its derivatives.

Recently, considerable interest has been aroused in the local use of sulfanilamide and its derivatives in the treatment of superficial infections. At the present time our knowledge concerning the true value of these compounds when used locally is meager. However, in our own experience, we have noted that streptococcal ulcers, indolent superficial staphylococcal infections, wounds and burns infected with mixtures of pathogenic microorganisms often clear up promptly when treated locally with powdered sulfanilamide or its derivatives. While no definite information is available regarding optimal amounts of sulfanilamide or its derivatives for local use, it has been suggested<sup>4</sup> that 0.10 gram per square inch of exposed tissue represents an adequate daily dose. On extensively debrided surfaces, this can be sprayed on easily with a pow-



TABLE IV

THE INDICATIONS FOR THE USE OF THERAPEUTIC ANTISERA  
WITH SULFANILAMIDE OR ITS DERIVATIVES

<i>Gas Gangrene—</i>	Adequate clinical data is not available.
<i>Meningococcal Infections—</i>	No conclusive clinical evidence that the combined use of meningococcal antiserum and sulfanilamide is better than sulfanilamide alone.
<i>Pneumococcal Lobar Pneumonia—</i>	Patients who are severely ill should receive <i>adequate amounts</i> of type specific pneumococcal antiserum as well as full doses of sulfathiazole.
<i>Staphylococcal Infection—</i>	Clinical evidence as to the value of combined therapy is not available.
<i>Scarlet Fever—</i>	Patients who are moderately or severely ill should receive <i>adequate amounts</i> of scarlet fever antitoxin as well as sulfanilamide.

der atomizer. It is probable that the main value of the local use of sulfanilamide or its derivatives is that it is possible to obtain relatively high concentrations of these drugs in the superficially infected tissues.

At the present time there is some controversy regarding the combined use of specific sera and antitoxins and sulfanilamide or its derivatives. In Table IV are given the indications for such combined uses. As may be seen from the table, only in patients severely ill with pneumococcal lobar pneumonia, or in patients moderately or severely ill with scarlet fever, is there definite information which leads us to believe that combined sero- and chemotherapy is of real value.

The indications for the prophylactic use of sulfanilamide or its derivatives have not been thoroughly established. In Table V we have listed the possible prophylactic uses of these drugs. It seems quite clear at the present time that the administration for a period of 10 days to 2 weeks of adequate doses of sulfanilamide (either perorally or locally) to patients suffering from compound fractures, prevents the development of gas gangrene and probably other types of infection. There also seems to be good reason to believe that if the earliest stages of otitis media (that of the beginning earache) are treated with sulfanilamide or sulfathiazole for a period of 48 to 72 hours, few children will develop purulent infections of the middle ear with the possible resulting train of complications. The observations of Ravdin and Lockwood<sup>5</sup> show quite

TABLE V

INDICATIONS FOR THE POSSIBLE PERORAL PROPHYLACTIC USE  
OF SULFANILAMIDE OR ITS DERIVATES

Sulfanilamide	Sulfapyridine	Sulfathiazole
Burns Compound Fractures Scarlet Fever Contacts when Dick Test Positive Extensive Tissue Injuries Accidental Operative Gunshot Wounds Otitis Media (Earache) Peritonitis (Appendectomies, Large Bowel Resections, etc.) Rheumatic Fever (Quiescent stage)	Otitis Media	Burns Peritonitis (Appendectomies, Large Bowel Resections, etc.) Urinary Tract Infections (Urological Operations)

clearly that the routine use of adequate doses of sulfanilamide in the postoperative treatment of appendicitis has markedly decreased the morbidity and case fatality rate from peritonitis occurring as a complication of appendicitis. Also the work of Thomas et al.<sup>6</sup> and of Coburn and his associates<sup>7</sup> seems to point to the fact that in the northern half of this country the administration of small daily doses of sulfanilamide from the first of October to the first of June prevents the recurrence of the active manifestations of rheumatic fever in patients suffering from that disease. If these latter observations could be widely confirmed, a most important prophylactic measure would be at our disposal.

The administration of sulfathiazole as a prophylactic agent to patients who are undergoing a resection of the large bowel, or who have the risk of developing peritonitis following operative procedures in the abdomen, has seemed to be most effective in The Johns Hopkins Hospital during the past year. In those patients who have to undergo a resection of the large bowel, the drug is started in doses of 1.0 gram every 4 hours on the afternoon prior to the day of operation and is continued until about the sixth postoperative day.

In Tables VI to X are shown the amounts of sulfanilamide or its derivatives which we believe represent therapeutically effective doses for severe infections due to the hemolytic streptococcus, the meningo-

TABLE VI  
THE DOSAGE OF SULFANILAMIDE

- 
- |  |                      |
|--|----------------------|
|  | <i>Sulfanilamide</i> |
|--|----------------------|
- 
- A. Severe Infections
- Initial dose (oral): 0.10 gram per kilogram of body weight.  
Subsequent doses (oral): Total daily dose based on 0.10 gram per kilogram, this to be divided in 6 parts and given Q.4 h. day and night until 7 days of normal temperature have elapsed.
- B. Mild and Moderately Severe Infections
- Total daily dose based on 0.10 gram per kilogram of body weight, this to be divided into 6 parts and given Q.4 h. day and night until 5 days of normal temperature have elapsed.
- C. Hemolytic Streptococcal otitis media, mastoiditis or osteomyelitis present a special problem because these infections involve bone. Sulfanilamide should be continued in moderate doses for at least 10 days after a *clinical* cure has been effected.
- 
- 

coccus, the Welch bacillus, the pneumococcus, the staphylococcus and the gonococcus, and for mild or moderately severe tissue infections in which therapy with these drugs is indicated. When one is prescribing sulfanilamide for the treatment of a severe infection, it is highly important to give a large initial dose in order that a therapeutically efficient concentration of the drug may be obtained rapidly; then sufficient doses of the drug should be given at 4 hour intervals in order to maintain and augment the effect obtained by the initial dose. In general, in severe infections in which sulfanilamide is being employed as the drug of choice, a concentration of the drug of 10 mgms. per cent in the blood should be maintained until a marked clinical improvement in the condition of the patient has been noted. Then the amount of the drug given each day may be slowly decreased. In milder tissue infections in which sulfanilamide is the drug of choice, concentrations of around 5 mgm. per cent of the drug should be maintained in the blood.

On the basis of our present knowledge, it seems as though sulfapyridine and sulfathiazole were equally effective in the treatment of pneumococcal pneumonia, with sulfathiazole generally being the drug of choice because it is less likely to provoke nausea and vomiting. During the febrile period of the pneumonia, the concentration of these drugs should be kept at 4 to 6 mgm. per cent in the blood of the patient.

TABLE VII

## THE DOSAGE OF SULFAPYRIDINE AND SULFATHIAZOLE

*Pneumococcal Pneumonia*

## A. Adults

Initial dose (oral) either drug. 4.0 grams.

Subsequent doses (oral) either drug. 1.0 gram Q.4 h. day and night until the temperature has been normal for 72 hours.

## B. Infants and Children

Initial dose (oral) either drug, 0.15 gram per kilogram up to 25 kilograms of body weight.

Subsequent doses (oral) either drug. Total daily dose is based upon 0.15 gram per kilogram up to 25 kilograms of body weight, this to be divided into 4 parts and given Q.6 h. day and night until the temperature has been normal for 48 hours.

*Staphylococcal Pneumonia*

## A. Adults and Children

Sulfathiazole is the drug of choice. If satisfactory response is not obtained, increase daily dose by 25 to 50 per cent. Continue until temperature has been normal for 5 days.

TABLE VIII

## THE DOSAGE OF SULFATHIAZOLE IN STAPHYLOCOCCAL INFECTIONS OTHER THAN PNEUMONIA

A. Chemotherapy should not be used for boils, mild furunculosis, etc.

B. *Adequate surgical therapy should always be used in conjunction with chemotherapy.*

## I. Diffuse staphylococcal cellulitis, lymphangitis, etc., in adults

Initial dose (oral): 4.0 grams.

Subsequent doses: 1.5 grams Q.4 h. day and night until the infection has ceased spreading. Then 1.0 gram Q.4 h. day and night for 7 days.

## II. Staphylococcal bacteremia in adults

Initial dose (oral): 4.0 grams

Subsequent doses: 1.5 grams Q.4 h. until the temperature has been normal for 48 hours. Then 1.0 gram Q.4 h. for 14 days. Then 0.5 gram Q.4 h. for another 14 days.

## III. Staphylococcal infections in infants and children

The initial and subsequent doses are reduced from those advised for adults in proportion to the weight of the infant or child.

TABLE IX

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THE DOSAGE OF SULFAPYRIDINE OR SULFATHIAZOLE  
IN THE TREATMENT OF GONORRHEA IN THE MALE

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Either drug may be used.

*First day dose:* 3.0 grams, i.e., 0.5 grams at 3 hour intervals six times a day.

*Subsequent doses* (2nd to 10th days): 2.0 grams per day.

If by the 5th day of treatment a marked improvement in symptoms and signs of the disease has not taken place, shift to the other drug and carry on as outlined above. If a shift in medication has been made and after 5 days marked improvement is not observed, *stop drug therapy* and begin *conservative local treatment*. In any event *do not continue treatment with these drugs beyond 15 days in patients suffering from gonorrhea*.

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TABLE X

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THE PARENTERAL USE OF SULFANILAMIDE OR ITS DERIVATIVES

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*Sulfanilamide*—To be used only when oral medication is impossible.

Initial dose: 0.10 gram per kilogram of body weight made up in a 1 per cent solution in sterile physiological saline or 1/6 molar sodium racemic lactate.

Subsequent doses: 0.05 to 0.075 gram per kilogram of body weight in a 1 per cent solution, Q. 6 to 8 h.

It is best to give solutions of sulfanilamide by the subcutaneous route. Oral administration of sulfanilamide should be started as soon as possible.

*Sodium Sulfapyridine* or *Sodium Sulfathiazole*—To be used only when oral medication is impossible or satisfactory concentrations of the drug cannot be obtained by oral administration.

Initial dose: 0.06 gram per kilogram of body weight of the sodium salt made up in a 5 per cent solution of *sterile, freshly distilled water*. *Do not try to sterilize by autoclaving or boiling*.

Subsequent doses: 0.03 gram per kilogram of body weight of the sodium salt in a 5 per cent solution repeated at about 6 hour intervals.

*Always give slowly (10-15 minutes) by the intravenous route.*

Oral administration of sulfapyridine or sulfathiazole should be started *as soon as possible*.

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In staphylococcal infections, with the possible exception of staphylococcal meningitis, sulfathiazole should always be employed. The exception of staphylococcal meningitis is the result of the observation that *sulfathiazole does not pass over readily into the spinal fluid*. This drug should not be used in the treatment of small boils, mild furuncles, etc., which result from superficial infections with staphylococci, because the risk of toxic manifestations from sulfathiazole is greater than the therapeutic results which may be obtained. *It is also of extreme importance to remember that adequate surgical therapy should always be used in conjunction with chemotherapy in the treatment of staphylococcal infections*, and that when an apparent marked improvement has taken place in a patient severely ill with a staphylococcal infection, if the drug is discontinued too early, a recurrence of the infection is very likely to happen. On the basis of present data, concentrations of 5 to 10 mgm. per cent should be maintained in the blood of patients who are severely ill with staphylococcal infections.

Sulfanilamide and the sodium salts of sulfapyridine and sulfathiazole may be given by the parenteral route. Sulfanilamide is best administered by the subcutaneous route, while sulfapyridine and sulfathiazole should always be given by the intravenous route. When these drugs are administered by these routes, it is always wise to begin the oral administration of the drug as soon as the patient's condition permits, because the peroral route of administration of these drugs is, in general, the most satisfactory.

In patients whose infections involve bone or bony tissue, the use of these drugs presents a special problem because a recurrence of the infection is liable to take place unless all foci of infection have been eliminated. For this reason again, adequate surgical drainage is important, and in such conditions as otitis media, mastoiditis or osteomyelitis, the administration of sulfanilamide or its derivatives should be continued in moderate doses for at least 10 days after a *clinical cure* has been effected. The non-observance of this rule has been, in a large degree, the cause of the unsuccessful use of these drugs in otitis media or mastoiditis and for the reported masking of the symptoms and signs of these diseases.

One of the curious results of the intensive clinical work that has been done with sulfanilamide and its derivatives and of the publicity derived following such investigations during the past four years, has been to make physicians overcautious about the possible toxic manifes-

TABLE XI

MANIFESTATIONS OF DRUG TOXICITY NOTED IN ADULTS TREATED WITH  
SULFANILAMIDE, SULFAPYRIDINE OR SULFATHIAZOLE

<i>Reaction</i>	<i>Sulfanilamide</i>	<i>Sulfapyridine</i>	<i>Sulfathiazole</i>
Nausea, vomiting	Fairly common	Frequent	Uncommon
Dizziness	Common	Common	Uncommon
Psychoses*	0.6%, occur early	0.3%, occur early	Rare
Neuritis**	Very rare	Not reported	Rare
Cyanosis	Very common, early and late	Faint, common, early and late	Uncommon
Acidosis*	1.9%, occurs at any time, rare if soda is used	Not reported	Not reported
Fever*	10%, generally 5th to 9th day, may occur 1st to 30th day	4%, generally 5th to 9th day, may occur 1st to 30th day	10%, generally 5th to 9th day
Rash*	1.9%, may take any form, generally 5th to 9th day, may occur 1st to 30th day	2%, may take any form, 5th to 9th day, may occur 1st to 30th day	5%, nodular type common, may take any form, 5th to 9th day
Hepatitis**	0.6%, early or late	Not seen, but reported	Rare
Leukopenia with granulocytopenia**	0.3%, early or late	0.6%, early or late	1.6%, early or late

\* Best to stop drug and force fluids.

\*\* Imperative to stop drug and force fluids.

TABLE XI [continued]

<i>Reaction</i>	<i>Sulfanilamide</i>	<i>Sulfapyridine</i>	<i>Sulfathiazole</i>
Acute agranulocytosis**	0.1%, occurs 14th to 40th day, common 17th to 25th day	0.3%, occurs 14th to 40th day, common 17th to 25th day	Not reported
Mild hemolytic anemia	3%, early and late	Rare	Not reported
Acute hemolytic anemia**	1.8%, occurs 1st to 5th day	0.6%, occurs 1st to 5th day	Very rare
Hematuria*	Not reported	8%, generally early	2.5%, generally early
Anuria with azotemia**	Not reported	0.3%, generally 1st 10 days	0.7%, generally 1st 10 days
Hyperleukocytosis*	Generally in presence of acute hemolytic anemia	Generally in presence of acute hemolytic anemia	Not reported
Injection of sclerae and conjunctivae**	Not reported	Not reported	4%, may occur with rash and fever, 5th to 9th day
Purpura haemorrhagica**	Not seen, but reported	Not seen, but reported	Not reported
Ocular and auditory disturbances**	Rare	Rare	Very rare
Jaundice**	With acute hemolytic anemia or hepatitis	With acute hemolytic anemia or hepatitis	With acute hemolytic anemia or hepatitis
Painful joints*	Reported	Not reported	Reported with rash, etc.
Stomatitis*	Rare	Not reported	Not reported
Gastrointestinal tract disturbances*	Bleeding rare, diarrhea uncommon	Rare	Very rare

\* Best to stop drug and force fluids.

\*\* Imperative to stop drug and force fluids.



tations of these drugs, while the patients, who read only of the "wonder drugs" in their local press, are clamoring for these agents whenever they have the mildest scratch in their throats or on their fingers. It is our opinion that we, as physicians, have been right in adopting a somewhat cautious attitude towards the use of these drugs, but we also feel that as our experience has grown, it is now possible for the average physician to use these drugs intelligently even in the home, and that he should not worry too much about their possible toxic manifestations.

In Table XI are given the various manifestations of drug toxicity as we have noted them in hospitalized adults. It is evident from this table that the toxic reactions resulting from these drugs are quite frequent, but that those which are dangerous are relatively uncommon. It is our opinion that while it is always advisable whenever possible to utilize every available means of laboratory control in following a patient receiving sulfanilamide or its derivatives, practically all of the toxic reactions associated with the administration of these drugs can be detected by the physician if he exercises careful clinical control over his patient.

Patients who are receiving sulfanilamide or its derivatives for the first time *should be seen at least once a day*, and at this time the attending physician should inquire as to how the patient feels, with special reference to the symptoms of headache, body-aching or malaise, because these symptoms are the precursors of many of the toxic reactions of sulfanilamide or its derivatives. In addition to the inquiries concerning the patient's symptoms, the physician should carefully examine the sclerae for the presence of jaundice, and the conjunctivae for injection or paleness. The presence of jaundiced sclerae with pale conjunctivae probably means that an acute hemolytic anemia is developing. If the conjunctivae are not pale, then the jaundice probably results from liver damage. The occurrence of injected conjunctivae and sclerae, together with smarting and burning of the eyes occurs as a toxic manifestation only in the course of sulfathiazole therapy. As an added check to the conjunctival examination, the oral mucous membrane should be looked at, and inquiry should be made as to whether or not the patient is developing a sore throat. If the patient has been treated with sulfanilamide or one of its derivatives for more than a week, and while under treatment develops a moderately severe sore throat, this may indicate the beginning of an agranulocytosis, because, if he is being treated adequately, it would be quite unlikely that he would be getting a hemolytic strepto-

coccal sore throat. The skin of the body should always be looked at carefully for the presence of rash, because frequently in the early stages of such a toxic manifestation, the patient or his attendants will miss the fine macular eruption in the skin. At this point we can stress the importance of keeping patients who are receiving sulfanilamide or its derivatives out of the direct rays of the sun and away from sources of ultraviolet light, because there is no doubt that a certain number of patients who develop a skin rash in the course of therapy do so because of a photosensitization. Any patient receiving these drugs should stay out of the sun until three days after he has stopped taking the drug, or until after the time when the drug has been completely excreted.

The temperature should always be taken in order to detect whether drug-fever is present, and if the patient says he has been having chills, and at the time that it is taken, the temperature is normal, arrangements should be made to have it taken frequently during the next 24 hours in order to determine whether or not fever is present.

Inasmuch as sulfanilamide does not directly damage the kidneys, no special precautions have to be observed in respect to the urine of patients who are receiving sulfanilamide, but it is very important that the urine of patients who are receiving sulfapyridine or sulfathiazole be looked at when freshly voided, and that the total urine output be measured daily. This can be done easily by the patient's attendants or family and a urine volume of at least 1000 cc. per day should be maintained. If the urine output starts to drop and the fluid intake has been properly maintained in patients who are receiving sulfapyridine or sulfathiazole, it is very good evidence that the drugs are damaging the kidneys either due to a direct toxic effect upon the kidney epithelium or as a result of mechanical blockage by aggregations of acetyl sulfathiazole or acetyl sulfapyridine crystals. However, in the face of a normal urine output, the presence of these crystals in the voided urine should never be considered an indication for stopping the drug. The appearance of gross blood in the urine at any time in the course of therapy with these drugs constitutes a good reason for stopping therapy.

Thus, it can be seen that, with the possible exception of leukopenia or agranulocytosis, all of the toxic reactions resulting from the administration of these drugs can be discovered if the patient is kept under careful clinical observation during his course of treatment, and for this reason it has proved highly practical for careful physicians to employ

these drugs in patients who are being treated in their homes. If toxic manifestations appear, these drugs should be discontinued and fluids should be forced vigorously in order to eliminate them from the system as rapidly as possible.

Finally, it must be kept in mind that if a patient has previously had a rash, drug-fever, hepatitis, leukopenia, acute hemolytic anemia, injection of the sclerae and conjunctivae, diarrhea or purpura hemorrhagica in the course of therapy with sulfanilamide or its derivatives, he is very likely to have a second, earlier and more severe toxic reaction if sulfanilamide or one of its derivatives is administered a second time. For this reason one must always ask a patient whether or not he has taken one of these drugs previously with a resulting toxic reaction, before prescribing any member of this series for a second time. If such a history is elicited, it is best to give a small test dose of the drug (0.15 to 0.3 gram) and then observe the patient for acute toxic manifestations over a period of 12 hours before beginning the course of therapy. If none is observed, treatment with the drug may be cautiously begun and continued, with a constant watch being kept for possible toxic manifestations.\*

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\* Certain of the dosage schedules which are given in this report are based upon those recommended by the Advisory Committee on Chemotherapeutic and Other Agents of the National Research Council.

## ELECTROPHORETIC ANALYSIS AND THE CONSTITUTION OF NATIVE FLUIDS

*Harvey Lecture, October 19, 1939*

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RECENT years of research in the borderland between chemistry, biology, and medicine have given us many new examples of a fact known since long ago; namely that the fundamental processes of life are intimately connected with chemical substances of large molecular weight. Only such substances are capable of the great variation and specificity which are considered to be characteristic of life itself. Among these substances proteins should be mentioned first, but we know now that large carbohydrate molecules also are capable of considerable variation in structure and biological properties. The nucleic acids present in the cell nuclei and in many virus proteins are probably in many cases large molecules. It is true that a considerable number of substances essential for life are of comparatively simple structure like the vitamins and many hormones. On the other hand, there is increasing evidence that these depend to a considerable extent for their activity on their interaction with large molecules, especially with proteins. Without proteins no life is possible. No wonder, therefore, that there has been an enormous concentration of efforts by scientists all over the world to contribute to our knowledge of the structure and reactions of these and other large molecules. The results gained so far, and particularly some of the more recent developments in this field, have been very encouraging as some of the most important processes in living organisms have been shown to depend upon specific proteins, which can be isolated in what seems to be pure state, as, for example, some of the enzyme proteins. Also there is considerable evidence that antibodies in immune sera are proteins, and the recent researches of Stanley and others have demonstrated that the same is true for certain viruses. Such fundamental phenomena as muscle contraction and growth have been interpreted as

protein reactions, and interesting attempts have been made to correlate morphology and chemical structure.

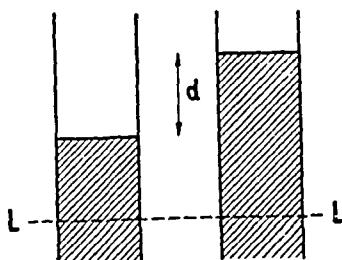
While watching the developments in this field of research during the last few years one is struck by the diversity in the modes of attack on the problems. Structural organic chemistry is, of course, still the basis for this research, as it was in Emil Fischer's time, and for proteins the recent work of Bergmann, Niemann, and their collaborators has brought us much new information along these lines. Many of the new contributions have also come from physical chemistry, and I think I am justified in mentioning here especially the name of my countryman and teacher, The Svedberg. But also physics, x-ray crystallography, spectroscopy, immunology, genetics, medicine, and even pure mathematics have contributed to the new advances. There is hardly any field in modern science where research is carried on at so many frontiers simultaneously.

I wanted to emphasize this fact particularly, as I am going to present to you tonight the development of and the results gained mainly by only one method, namely, by electrophoresis, since the president of the Harvey Society has been kind enough to ask me to tell you something about the recent developments in this field. Here as well as in other fields of protein chemistry the most significant results have been obtained by combining evidence gained by a number of different methods.

Electrophoresis, that is the migration of colloidal particles in an electric field, has been known and studied by physical chemists for the past 100 years. It first became of significance for biochemistry, however, in 1899, when Sir William Hardy<sup>1</sup> observed that proteins show this phenomenon in a highly characteristic way and that their migration velocity depends upon the acidity of the medium. Among the early work in this field mention should be made especially of the investigations by Michaelis and his collaborators, which demonstrated the value of the method for the characterization of enzymes and proteins by their mobilities and their isoelectric points.

The most direct method of studying electrophoresis, namely the observation of the migration of individual particles in a solution with the microscope or the ultramicroscope is, unfortunately, very limited in its application, as most of the substances which are of interest have such a small molecular or particle size that they are beyond the resolving power of any microscope. The observation of electrophoretic migration must, therefore, depend upon measurements of the movement of a layer

## Electrophoresis Methods:



Moving Boundary: distance  $d$  measured

Transference: increase in quantity of substance  
above  $L$  measured

Fig. 1—Diagram of electrophoresis methods.

of the solution of the substances in the electrophoresis tube. For this purpose two different methods have been used (Fig. 1); one, the transference method, depends upon the determination by chemical or biological analysis of the increase or decrease of the amount of substance above a fixed level in the tube, when a known amount of electricity is sent through, the other, the moving boundary method, measures the distance traveled by the boundary between the solution and a supernatant medium of the same composition with respect to the electrolytes. The former method has been used particularly for studying enzymes; the latter is especially convenient for colored materials. Both methods are, of course, in principle identical with those used by the physical chemists for measuring migration velocities of ordinary ions.

Svedberg, in his first studies of the ultracentrifugation of proteins, made use of their strong absorption in ultraviolet light to observe their sedimentation. The application of the same technique to observe the moving boundaries in the electrophoresis tube was tried by Svedberg and myself in 1926 with some success.<sup>2</sup> In this way the moving boundary method could be applied also to colorless substances. The improved possibilities of observing what was happening in the electrophoresis tube showed, however, that the electrophoretic migration suffered from several disturbances. A detailed study of these phenomena and a description of an improved apparatus was published in 1930<sup>3</sup> together with measure-

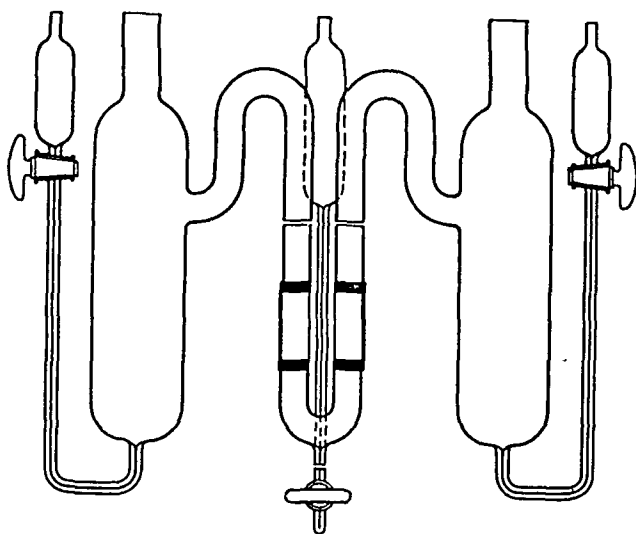


Fig. 2—Electrophoresis apparatus for observation of the migration by photography in ultraviolet light.

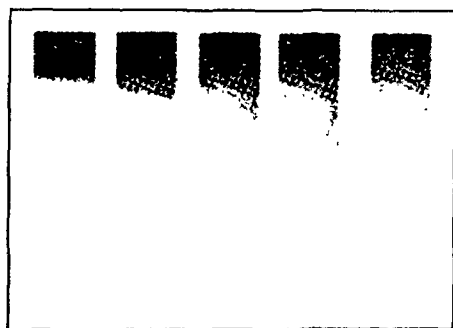


Fig. 3—The separation of egg albumin and Bence-Jones protein observed by ultraviolet light photography.

ments on a number of comparatively well-defined proteins (Fig. 2). One important improvement in the new type of apparatus was the introduction of large volumes of buffer solution in the electrode vessels to protect the protein boundaries from being reached by the disturbances which inevitably occur at the electrodes. Figure 3 shows a series of successive photographs of one limb of the tube when a mixture of egg albumin and Bence-Jones protein was studied. It demonstrated the possibility of using the method as a tool for studying unknown mixtures, and perhaps also the application for separation purposes. Of course, the most obvious importance of electrophoresis is the determination of

mobilities and isoelectric points for the purpose of characterization, and, if possible, for the calculation of the charge, and a large number of determinations of this kind have already been made in Upsala as well as in other laboratories. However, the application of the method for the study of mixtures and for preparative purposes is of particular importance for some of the problems I am going to discuss this evening.

The electrophoretic separation of the two proteins in Figure 3 suggests a more general application, but it is well known to everybody working in this field that in most cases great difficulties are encountered. No doubt the possibilities of electrophoretic separation have been realized for a long time. These difficulties may, however, be one reason why procedures of this kind have come into use only slowly in the biochemical laboratories. Another reason may be that the particularly great value of gentle methods for isolation of biologically important large molecules has been realized only lately. The successful use of adsorption, chromatographic analysis, ultrafiltration, and ultracentrifugation in the study and fractionation of mixtures of large molecules as they occur in nature has been one of the most striking and important recent developments in the methods of biochemistry. Early attempts to make use of electrophoresis for similar purposes (purification of pepsin) were made by Ringer,<sup>4</sup> and the method also soon found certain applications in industry (purification of gelatin). More recently Theorell, who has contributed much to the improvement of electrophoresis methods, was able to isolate Warburg's yellow enzyme this way,<sup>5</sup> and similarly du Vigneaud and his collaborators obtained a considerable fractionation of the hormones of the pituitary gland.<sup>6, 7</sup>

During the last few years in the Upsala laboratory several improvements in the technique of electrophoresis have been made<sup>8</sup> which considerably increase the efficiency of the separation and appear to widen the scope of the method to a large extent. The immediate reason for these attempts was the desire to study sera and a number of other native fluids. These are mostly characterized by a comparatively high conductivity on account of the large amount of salts present. Also in other cases large amounts of electrolytes are necessary to ensure a disturbance-free migration. Perhaps the greatest difficulty in electrophoresis is caused by the heat generated by the current. In solutions of considerable salt concentration this will give rise to convection currents which will stir up the solution in the tube and may entirely spoil the boundaries.



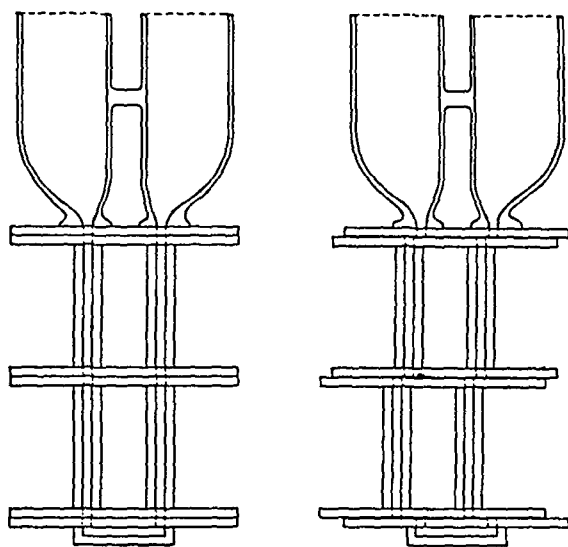


Fig. 4—The assembled U-tube of the new electrophoresis apparatus.

Fortunately, there is a comparatively simple way of eliminating this difficulty to a large extent. Water and solutions in water have a density maximum near  $+4^{\circ}\text{C}$ ., that is, the density variation which accompanies a rise in temperature and which is responsible for the convection will be negligible if the electrophoresis tube is kept in the neighborhood of this temperature. The apparatus is immersed in a bath which is kept about one degree above zero, and with maximum current the temperature in the tube rises to about the right value. The electrophoresis tube itself is built up of glass cells of rectangular cross section ( $25 \times 3\text{ mm.}$ ) with optically plane walls (Fig. 4). These cells can be made to slide over one another, thus separating the contents of the U-tube into five samples (right in Fig. 4). The sample under investigation is filled into the bottom and the lower of the middle compartments, the latter is moved out to one side, and the upper part is filled with a buffer solution of the same composition as that of the sample (usually they have been dialyzed against each other before filling the cells). By sliding the lower middle cell back into alignment with the others the boundaries are formed. The necessary back and forth movements of the cell are performed with small air pressure pumps, shown right and left in Figure 5, which also shows the U-tube mounted in a metal stand. Figure 6 is a diagram of the complete apparatus immersed in the bath (the cooling

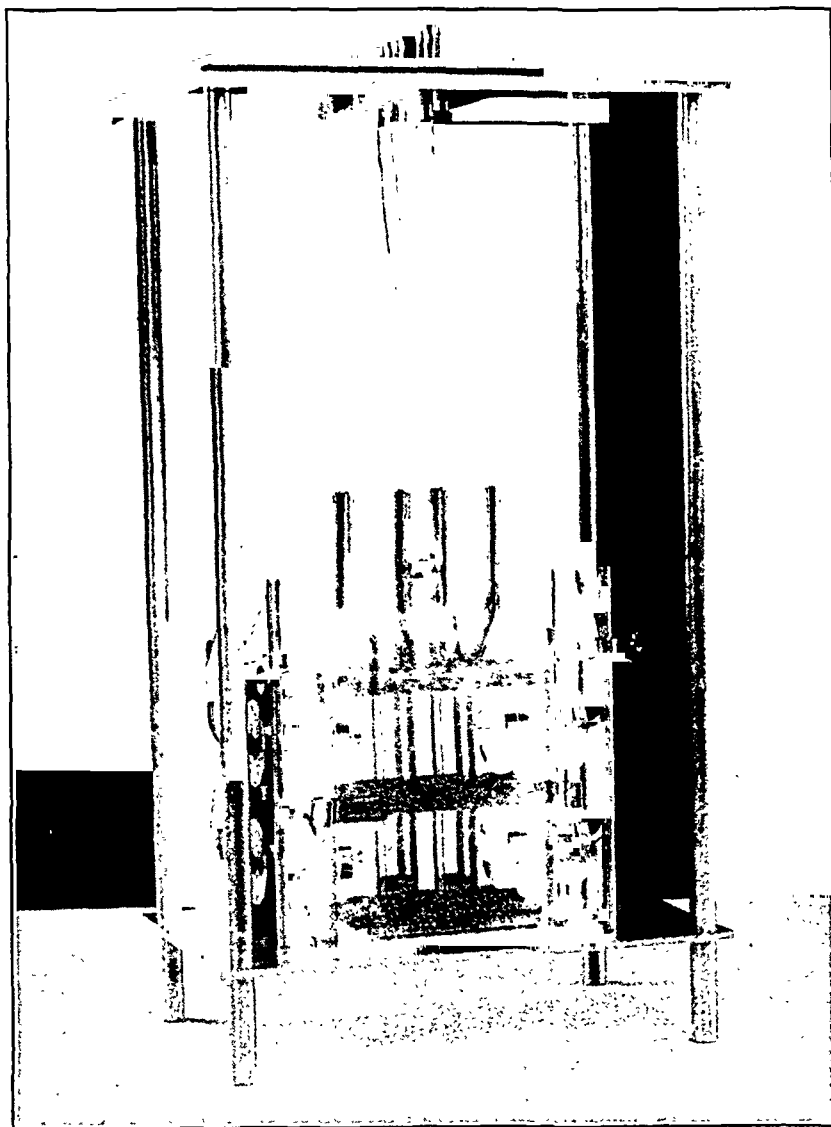


Fig. 5—The U-tube mounted in a metal stand.

coil is seen on the right). The U-tube has been connected to electrode tubes (as in the apparatus in Fig. 2), which contain reversible silver-silver chloride electrodes (not shown in the figure).

The apparatus as now described may be used for migration determinations by the transference method or for separation purposes. Its capacity is 10-11 cc. After a sufficient migration or separation has been obtained the U-tube is divided up, as in Figure 4 (right), so that the

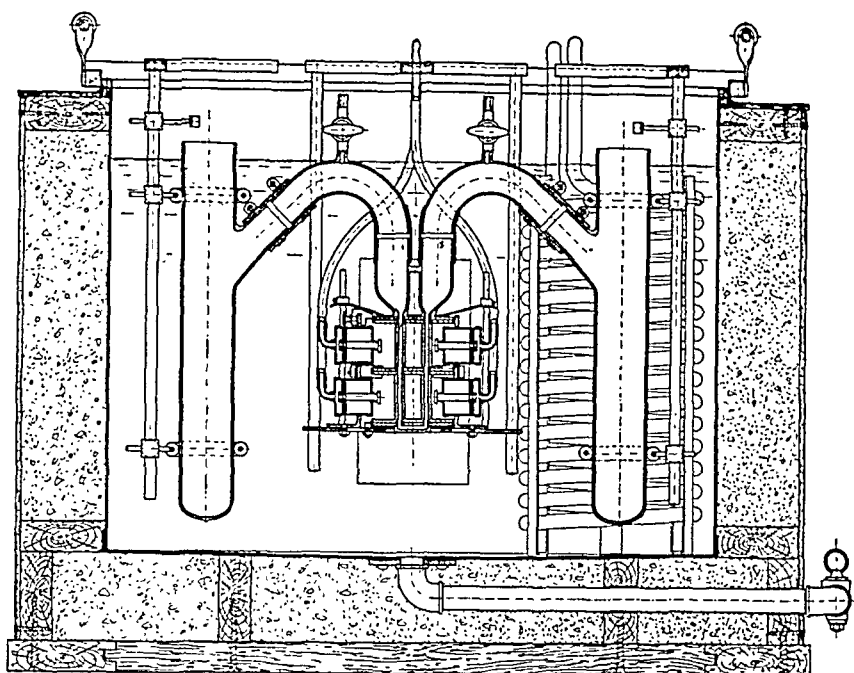


Fig. 6—Complete apparatus in low temperature bath.

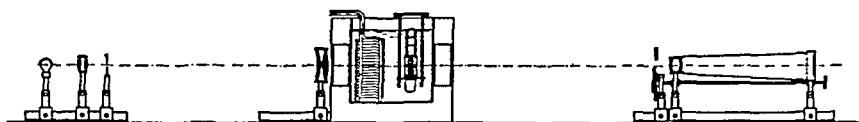


Fig. 7—Optical arrangement for observation of electrophoresis by the schlieren method.

different portions may be obtained separately for analysis or for further investigation. However, the optical observation of the migration has many advantages, especially when dealing with unknown mixtures, and also for convenient mobility measurements. Instead of the ultra-violet absorption, a method depending upon refractive index was introduced which proved to be much superior both in accuracy and convenience. This method, the Toepler schlieren method, has found extensive use for detecting small inhomogeneities in refractive index, for example in testing optical glass, and can be made extremely sensitive. The arrangement used for electrophoresis observation is shown in Figure 7. The apparatus is seen mounted in the bath, and the cells can be observed or photographed with the camera (right). The illumination



Fig. 8—Schlieren photographs of the migration of egg albumin.

system consists of a horizontal slit (left) an image of which is projected onto the camera lens by a large objective close to the apparatus. An adjustable horizontal knife edge at the camera lens will normally admit all light which passes through the electrophoresis tube into the camera. If, however, there is a refractive index gradient somewhere in the tube, as is the case at each boundary, light passing through this level will be deviated downwards and screened off by the knife edge so that the corresponding part of the image of the U-tube in the focus of the camera will receive no light from the illumination system. The boundaries will, therefore, appear as horizontal black bands in this image, and may be observed visually on the screen or photographed, making an exact determination of their position in the tube possible. The width of the schlieren bands depends upon the homogeneity of the migrating substance and, to a certain extent, on the setting of the diaphragm.

Figure 8 shows a number of exposures obtained in one of the first experiments (migration of crystalline egg albumin). For the subject of this lecture it is particularly important to notice the good definition of the position of the boundary, which greatly improves the possibility of studying mixtures. This was confirmed by actual experiments, using a number of artificial mixtures of different proteins. It was also obvious that by using the optical method as a guide, a separation of small quantities could be effected, the contents of the electrophoresis tube being divided into samples at the end of a run in the way shown in Figure 4 above.

I have described these improvements in the method to you in some

detail as I believe that in this field it is extremely important to use a satisfactory experimental technique. Electrophoresis experiments badly conducted will not only give incomplete or uncertain information; they may give very definite information which is entirely false. On the other hand, it is obvious that one does not take the trouble to concentrate his efforts on the improvement of a method unless there is some reason to believe that it will be of importance for the kind of research we are engaged in. I have already emphasized the importance of the application of gentle methods in work with large molecules obtained from native material, and I should like to add a few more words on that point. When a substance is obtained from such material, for example, by extraction and precipitation with salts or with organic solvents, the question which always occurs is: Does this substance also occur in the native material, or have we modified its properties in any way by our method for its isolation? Any one who has done work of this kind will, I believe, recognize the difficulty. To take an example, there is no doubt if we precipitate a protein in this way, containing some carbohydrate or some lipids or nucleic acids, that all the substances obtained occur in the original material; but the question is; Do they occur together in mutual combination or are they free from each other? The importance of that question has been gradually realized in biochemistry as we have learned that even very weak forces acting between molecules may have a profound influence on their chemical and biological properties. We know that a toxin is neutralized by its specific antitoxin, forming a very unstable complex which may even be partially dissociated by dilution of the solution, and similar conditions seem to hold for the neutralization of viruses by specific substances. We also know that prosthetic groups, of different kinds, nucleic acids and carbohydrates may modify the biological properties of proteins in an essential way. We have every reason to believe that life itself, to a large extent, must depend upon very delicate structures, as yet unknown to us but characterized by the linking together of the various essential molecules in a highly specific and characteristic way. It is conceivable that such structures would be destroyed by many of the drastic procedures usually employed in chemical work. With gentle methods there is at least some chance that the constituents isolated will correspond more closely to those in native conditions. In this connection it may be of interest to observe that already we have some indication that materials obtained by such methods

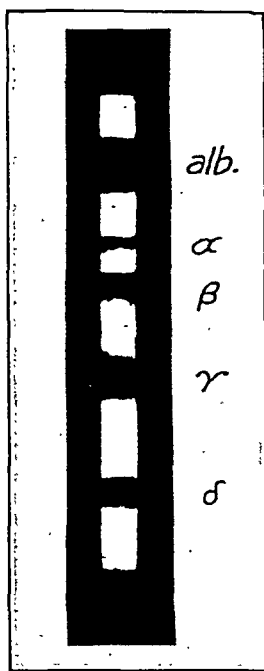


Fig. 9—Electrophoresis of horse serum.

or studied *in situ* in the organism show regularities which may not be found with degraded material. I am thinking especially of the molecular size and homogeneity of proteins as found by Svedberg and his collaborators and of the results obtained by Astbury and others by x-ray methods, showing that crystalline, or at least semicrystalline, structures occur frequently in organisms.

I have already mentioned that the immediate reason for our attempts to improve electrophoresis methods was our intention to study blood serum in this way. The present views of the constitution of this fundamentally important fluid vary a great deal, depending mainly upon the methods used for its study and, in particular, its fractionation into protein components. It has been assumed by some that serum contains essentially only one protein molecular species, the "serum molecule" (Block<sup>9</sup>), and by others a large number of different proteins which cannot be distinguished sharply on account of their mutual interaction (Sørensen<sup>10</sup>). By ultracentrifugation two main components were found to be present and were identified as albumin and globulin.\* Our first

\* As found recently by Pedersen, molecular size is not a suitable property by which to distinguish between albumin and globulin as part of the serum globulin may assume the molecular weight of albumin.

experiments using the earlier type of apparatus (Fig. 2) with serum globulin, which had been found homogenous with respect to its molecular size, gave definite evidence that it was inhomogenous electrophoretically, but the resolving power of the method was too low to give any more detailed information. The first experiment with the improved method (Fig. 9), obtained with horse serum showed the presence of a number of distinctly different components which were isolated by separation.<sup>8, 11</sup> As only the fastest of these was not precipitated by half saturation with ammonium sulphate, this substance was identified as albumin and the rest as globulins, and these were named  $\alpha$ ,  $\beta$ , and  $\gamma$  globulins. The  $\delta$ -boundary in Figure 9, which remains at the position of the original whole serum boundary and does not migrate, does not represent a component but depends upon an inhomogeneity in the conductivity of the medium which is to be expected in concentrated protein solutions and may be accounted for theoretically (see for example Henry and Brittain<sup>12</sup>). Similar diagrams have been obtained with sera from other species, including human beings. Human plasma was shown by Stenhagen to contain an additional component which was identified as fibrinogen since it disappeared on clotting.

In order to study the chemical characteristic of these components it was necessary to isolate them in large quantities; the method used for this purpose will be described below. The results obtained by Blix and Svensson (to be published shortly) for the lipid contents are of particular interest.

Globulin  $\beta$ : 4.6—12.7 per cent cholesterol, 0.31—0.46 per cent lipid phosphorus  
Globulin  $\gamma$ : 0.71—0.86 per cent cholesterol, 0.03—0.05 per cent lipid phosphorus  
(in normal human sera)

These figures show that the  $\beta$ -component has a high affinity for phosphatides or that the phosphatides move with a mobility close to that of  $\beta$ -globulin. The fat globules in serum move with the  $\beta$ -boundary. They are probably surrounded by an adsorbed layer of  $\beta$ -globulin. In horse sera the boundaries are considerably less distinctly separated than in human, rabbit, and cow sera. Even for these, however, it does not seem likely that each component represents a definite chemical individual, especially since the  $\gamma$ -boundary is mostly rather broad, and also for the others it seems more reasonable to assume that they are groups of similar proteins with each group well distinguished from the others. It is quite likely that a higher resolution will split the components further. We

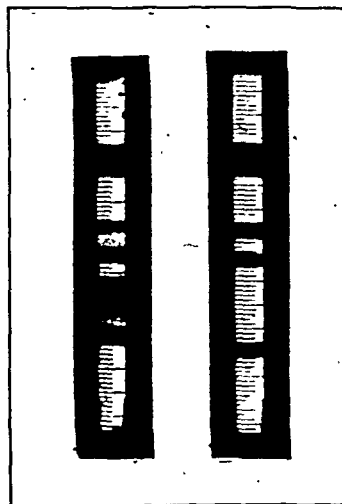


Fig. 10a—Electrophoresis of antipneumococcus horse serum.

plan to increase the separation by using a cell of twice the normal length to study this problem further. Until this has been done and until protein components obtained from serum by other methods have been compared with ours, I think it is too early to try to give a more complete description of the constitution of serum, not to mention an agreement upon a suitable terminology.

It is obvious that a vast field remains to be explored by these methods: for example, a comparative study of the sera throughout the animal kingdom, the development of the serum constituents in an individual with age, changes in pathological cases and during immunization. So far a number of exploratory investigations have been made both in Upsala and elsewhere, and I shall report on some of the results. It should be remembered, however, that the full significance of the results will not be understood until more is known about the normal sera in a few well-defined cases, especially regarding the chemical characterization. The fact that in these diagrams only the mobility is used for the definition of the components makes the evidence obtained somewhat limited in a complicated mixture like serum, as it seems quite likely that different constituents may have almost the same mobility at the pH commonly used for these studies. Figure 10a (Tiselius and Kabat<sup>13</sup>) shows the electrophoretic patterns obtained with a horse antipneumococcus serum before (left) and after (right) removal of the antibody by precipitation



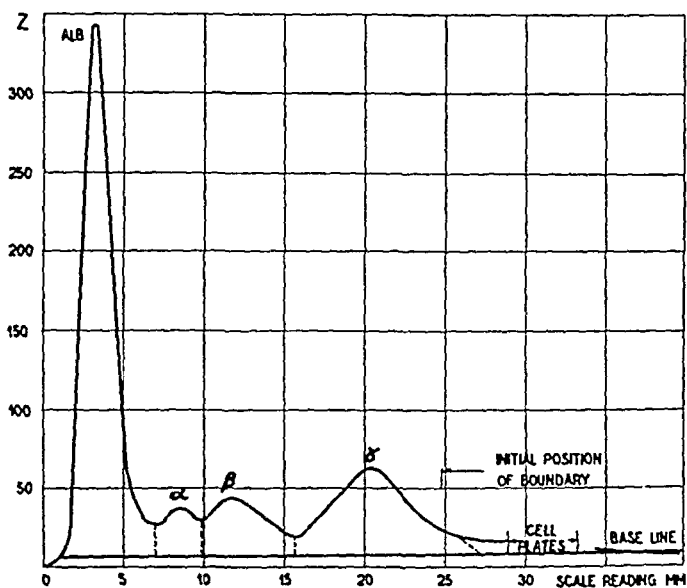
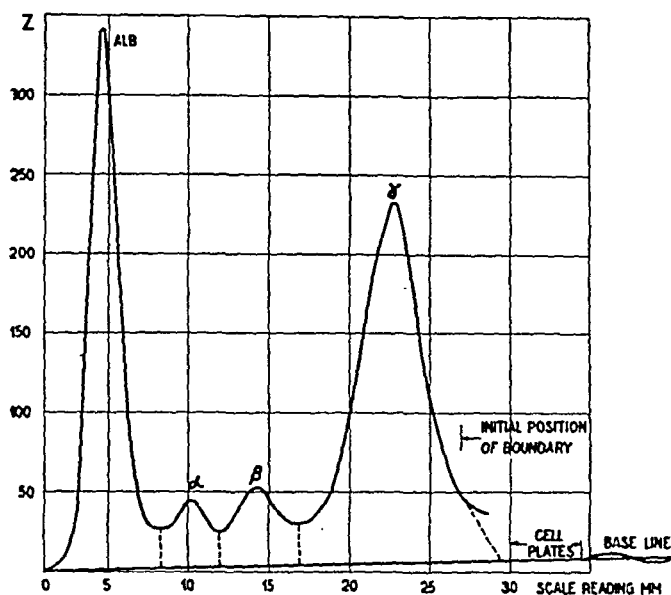


Fig. 10b—Electrophoresis of anti-egg albumin rabbit serum (upper curve) and normal rabbit serum (lower curve).

with the homologous polysaccharide. In this case the antibody globulin, therefore, appears to be electrochemically distinct from the other globulins. This is in agreement with the finding<sup>14, 15</sup> that its molecular weight is much higher than that of normal serum globulin. With rabbit antisera, however (Fig. 10b), the antibody in the cases studied showed up as an increase in the  $\gamma$ -fraction, not as a separate boundary and had the

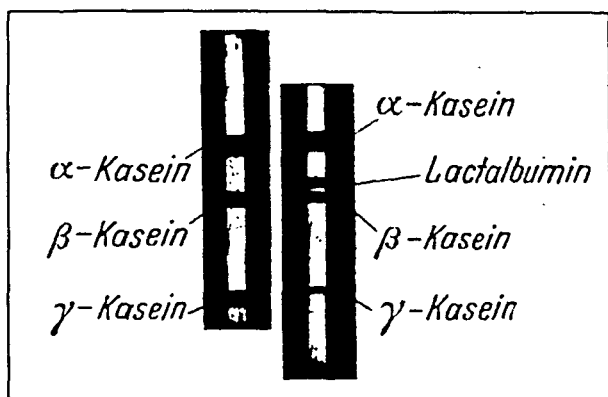


Fig. 11—Electrophoresis of casein (left) and of milk (right).

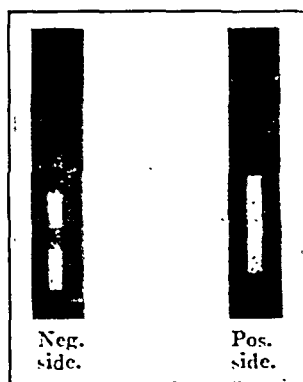


Fig. 12—Electrophoresis of crystalline lens extract (after 35 min.).

molecular weight of normal globulin. This is also the case with some horse antisera when the horse has been under immunization for a long period (Tiselius and Kabat<sup>13</sup>) as has recently been confirmed by Moore, van der Scheer and Wyckoff.<sup>16</sup> It should be emphasized, however, that the normal  $\gamma$ -globulin shows inhomogenous migration and a low mobility so that even a marked difference between normal and antibody globulin may not show up with the method described.

Another case of electrophoretic analysis of native fluids is shown in Figure 11, from experiments by Mellander.<sup>17</sup> It shows the electrophoretic pattern obtained with dialyzed milk (right) as compared to that obtained with a solution of casein, purified according to Hammarsten. Three casein components ( $\alpha$ ,  $\beta$ ,  $\gamma$ ) were observed in both cases, and the milk

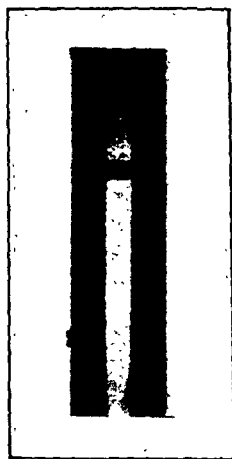


Fig. 13—Electrophoresis of vitreous body extract (after 35 min.).

diagram also shows the presence of lactalbumin. An investigation of a water extract of the crystalline lens (Hesselvik<sup>18</sup>) showed the presence of two proetins (Fig. 12) which could be identified as  $\alpha$ - and  $\beta$ -crystallin first isolated by Mörner.<sup>19</sup> Hesselvik also studied filtered vitreous bodies (Fig. 13) which demonstrated the presence of serum albumin,  $\gamma$ -globulin and a mucoprotein: hyalomucoid, moving faster than the albumin. Many other cases have been studied (see for example Hesselvik<sup>20</sup>), but these may be sufficient to demonstrate the application of the method in the study of mixtures for determining the number of components present and characterization of these components by their mobilities.

Considerable refinements have recently been introduced in the method of optical observation of electrophoresis, similar to those used in the work with the ultracentrifuge. The schlieren diagrams just demonstrated are sufficient to localize the components but do not yield all the information which may be gained from a more complete knowledge of the concentration distribution in the electrophoresis tube, unless a large number of observations are made with different settings of the schlieren diaphragm. A very accurate but somewhat laborious method for studying the concentration gradients was worked out by Lamm several years ago<sup>21</sup> and has found extensive use in diffusion and ultracentrifugation work. It has also been used to some extent in electrophoresis work by several investigators (Annetts;<sup>22</sup> Tiselius and Kabat;<sup>13</sup> Tiselius and Horsfall<sup>23, 24</sup>). Lately, similar methods, also depending

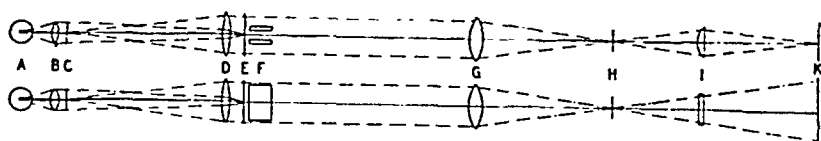


Fig. 14—Diagram of the Philpot-Svensson method for observation of concentration gradients. Upper half of diagram shows arrangement viewed from above, lower half from the side. *A*, lamp; *B*, condensing lens; *C*, slit; *D*, schlieren lens; *E*, screen; *F*, electrophoresis cell; *G*, camera lens; *H*, tilted slit; *I*, cylindric lens; *K*, photographic plate or screen.

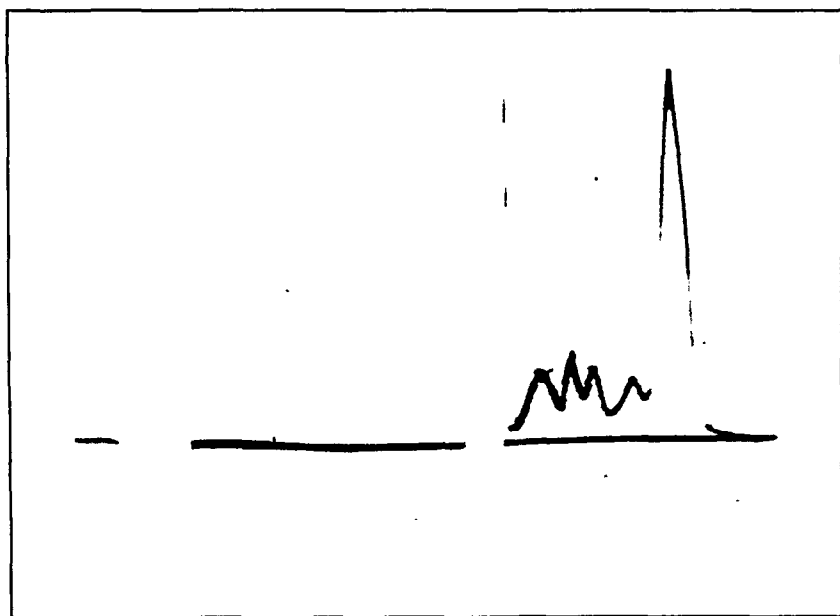


Fig. 15—Diagram of the electrophoresis of human serum obtained by the Philpot-Svensson method.

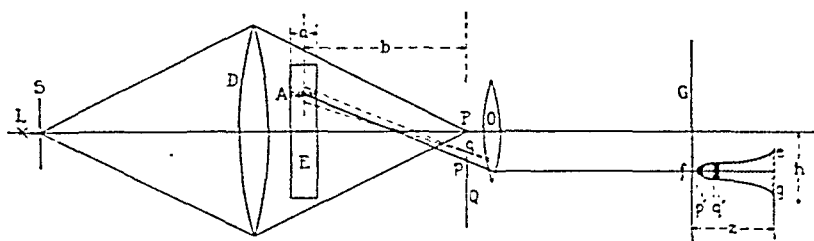
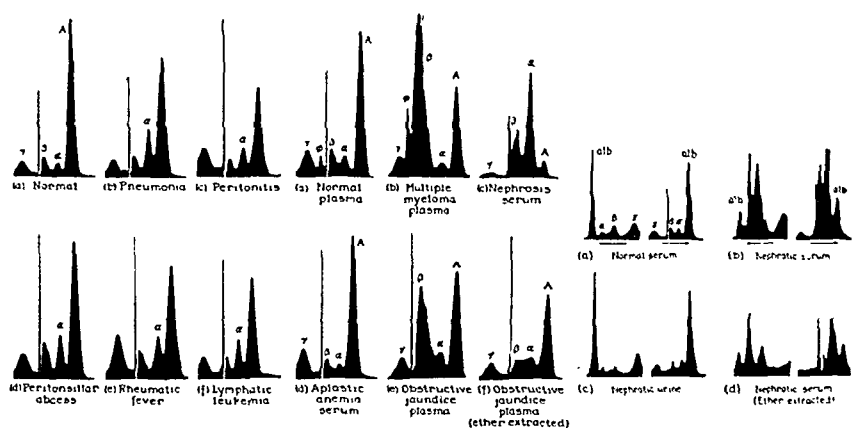


Fig. 16—Diagram of Longsworth's "schlieren scanning" method. *L*, lamp; *S*, horizontal slit; *D*, schlieren lens; *E*, electrophoresis cell; *Q*, schlieren diaphragm, the movement of which is mechanically coupled to the movement of the plate, *G*, at right angle; *O*, camera lens.



Figs. 17, 18, 19—Electrophoresis diagram of normal and pathological sera and plasmas (from Longworth, Shedlovsky and MacInnes<sup>29</sup>).

upon refractive index although considerably simplified, have been worked out by several investigators (Philpot;<sup>25</sup> Longworth;<sup>26</sup> Pickels; Andersson;<sup>27</sup> Svensson<sup>28</sup>). Figure 14 shows the arrangement by Philpot, somewhat modified by Svensson, now in use in the Upsala laboratory, and Figure 15, a diagram obtained from human serum by this procedure. Such curves are obtained directly in the focus of the camera and may be observed during the experiment and photographed. Each peak corresponds to a schlieren band, and the area under each peak is proportional to the amount of the corresponding component. Thus, a quantitative electrophoresis analysis can be made, and a much more detailed comparison between diagrams is made possible. The curves may demonstrate the presence of insufficiently separated components in a much more sensitive way than the simple schlieren photographs. Longworth's arrangement is shown in Figure 16. It depends essentially upon a mechanically coupled simultaneous movement of the photographic plate in the focus of the camera, and the schlieren diaphragm in front of the camera lens. The method has already been applied to a detailed investigation of a number of pathological human sera and plasma (Longworth, Shedlovsky, and MacInnes<sup>29</sup>). Figures 17, 18 and 19 show some of the results obtained. It was found that normal sera showed good agreement and gave reproducible results. A group of pathological sera was characterized by an abnormal increase in the  $\alpha$ -globulin (Fig. 17). Some similar observations had been made by Blix<sup>30</sup> using Lamm's method for recording the diagrams. Figure 18 shows some additional

diagrams, obtained by the first mentioned authors, where still more striking changes can be seen, involving an increase of the  $\beta$ -fraction (or a fraction of the same mobility) and in the case (c), a striking decrease in the albumin and increase in the  $\beta$ -globulin. Of the diagrams in Figure 19, obtained from a case of nephrosis, a comparison of (b) and (c) with (a) shows how the pathological urine proteins resemble those in normal serum, whereas the serum itself differs strikingly. Ether extraction in this and other cases (Fig. 18) shows that part of the abnormal increase in the  $\beta$ -fraction is due to ether soluble material, probably lipoids.

It is evident that the electrophoresis method is able to yield much more detailed information on the constitution of pathological sera than the usual precipitation methods. It will be of great interest to correlate the results with those recently obtained by Kendall,<sup>31</sup> using immunological reactions for the characterization of the serum proteins. It seems that still more detailed information might be obtained if the resolving power of the method could be increased as some of the peaks show a tendency to split up further. With this aim in mind, a cell of twice the usual length is now being constructed especially for serum work.

In the diagrams just shown (Figs. 17, 18, 19), which were obtained from the descending side, a disturbance is observed at the  $\beta$ -boundary, showing up as a very narrow and sharp peak. The nature of this is not yet clear. Possibly some precipitation takes place on account of the removal of albumin and  $\alpha$ -globulin on this side from the  $\beta$ -boundary, indicating that the presence of these proteins is necessary to keep some of the serum constituents in an unchanged state. It is a general experience from our work with serum that the  $\beta$ -component is the most unstable of all the serum constituents and is very difficult to isolate.

It is evident that electrophoretic analysis should be capable of giving some information also regarding reactions taking place between components in mixtures. It has been possible to demonstrate that in serum the pigment, bilirubin, is attached to the albumin (Bennhold;<sup>32</sup> Pedersen and Waldenström<sup>33</sup>). Smetana has shown that a number of dyes combine with denatured but not with undenatured proteins (unpublished work). Figure 20 shows an electrophoretic diagram obtained with a mixture of egg albumin and anti-egg albumin in the inhibition zone (excess of egg albumin, precipitate dissolved). The fastest boundary is the excess egg albumin, the slower is the complex between egg albumin and antibody globulin, moving at a rate intermediate between that of each

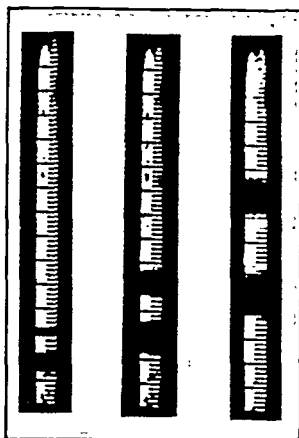


Fig. 20—Electrophoresis of a mixture of egg albumin and anti-egg albumin.

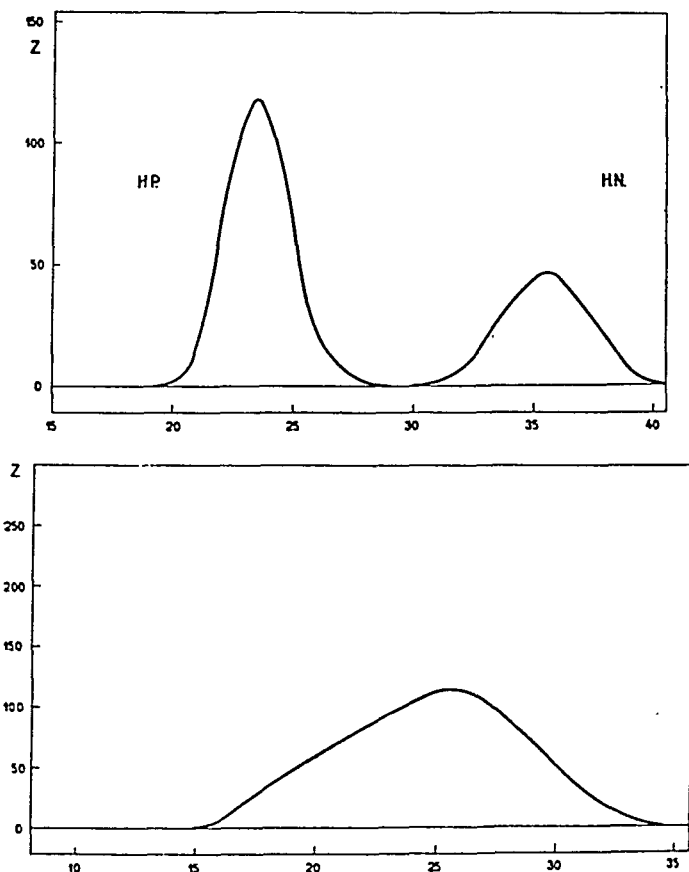


Fig. 21—Electrophoresis of a mixture of *Helix pomatia* and *Helix nemoralis* hemocyanins before (upper curves) and after (lower curves) cross combination by reversible dissociation-association.

component alone (Tiselius and Kabat, unpublished work). Figure 21 gives curve diagrams obtained from a mixture of hemocyanins from two different snails: *Helix pomatia* and *Helix nemoralis*. The upper diagram was obtained after mixing the two proteins, the lower after producing a reversible dissociation-association by shifting the pH to alkaline reaction and then bringing it back to the original value. This is sufficient to cause a formation of a series of cross compounds, a number of mixed molecules with properties intermediate between those of the two original native proteins (Tiselius and Horsfall<sup>23</sup>). Such cross combination, however, seems likely to occur only with the largest protein molecules, which are known to dissociate easily, and, moreover, only with biologically related substances.

In the course of preparation of pure proteins from native material the electrophoresis diagrams are often very helpful as a guide, to show how the preparation proceeds and the degree of homogeneity of the resulting products. This application reminds one of the use of spectrum analysis in chemistry for the detection and isolation of new substances. The spectrum-like appearance of the schlieren photographs is actually more than a superficial analogy. However, in a number of cases the preparative separation by use of electrophoretic migration itself has sometimes proved extremely useful, especially for the isolation of very unstable compounds and for the removal of impurities which are difficult to get rid of by other methods, particularly precipitation. It has been possible to separate the serum components this way, except perhaps for the  $\beta$ -globulin (Tiselius;<sup>11</sup> Tiselius and Svensson, to be published shortly), and to isolate carbohydrates from proteins in tuberculin preparations (Seibert, Pedersen, and Tiselius<sup>34</sup>), just to mention two examples. In enzyme chemistry this method seems to be of particularly great importance as shown especially by Theorell in his purification of Warburg's yellow enzyme and recently also of cytochrome c.<sup>35</sup> It has often been found that traces of impurities which still remain after other purification methods have been applied can be removed by electrophoresis (see for example also the purification of heparin by Wilander<sup>36</sup>). This circumstance may become of particularly great importance in the preparation of substances for immunological work when a trace of an impurity of a large molecule may be of decisive importance. It is a remarkable characteristic of the method that it is almost independent of the relative proportions between the components; the difference in



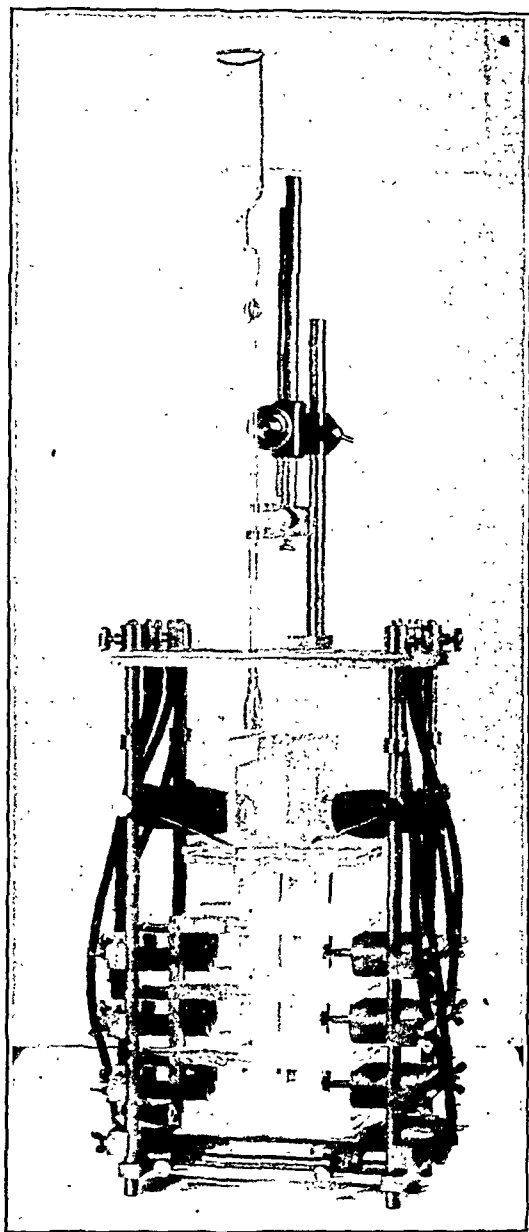


Fig. 22a—Large electrophoresis apparatus for preparative work.

the mobilities is the only decisive factor for the efficiency of the separation. It should be emphasized, however, that if the components combine partially in the solution, the separation will be incomplete also by this method. One should then look for a medium in which the compounds are likely to dissociate, for example extreme pH values.

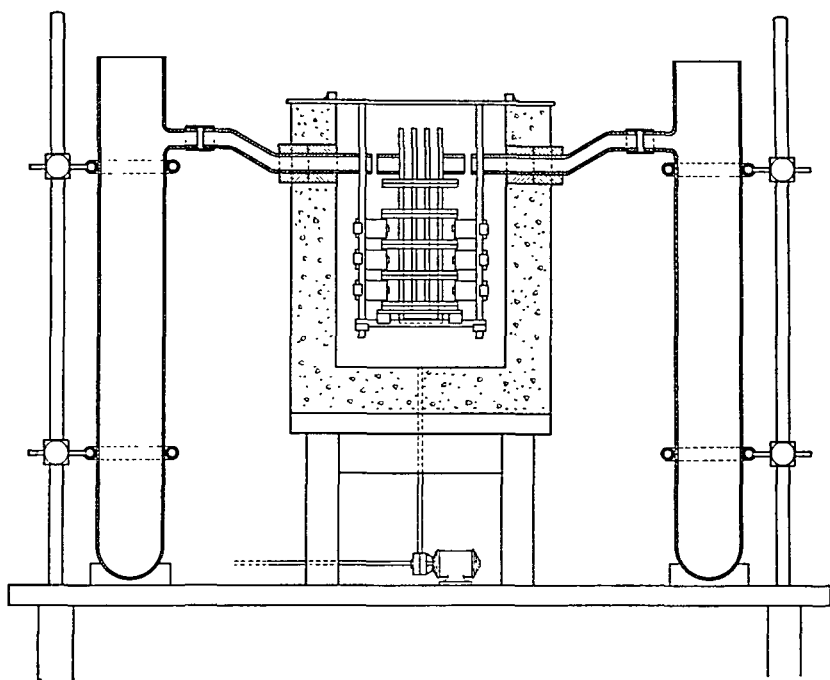


Fig. 22b—Large apparatus mounted in the bath, with the electrode vessels outside.

Even though successful separation may be obtained with the apparatus described, its capacity is too small for many purposes, the volume of the sample being only 10 cc. The value of electrophoretic methods for preparative work has been realized by many investigators, and several types of apparatus have been used, as has already been mentioned. For our purposes it has appeared essential to control the separation by optical observation, and an apparatus for this purpose taking 200-300 cc. is shown in Figure 22a. It has been built according to the same principle as the smaller type, with some modifications.<sup>37</sup>

The cross-sectional area is ten times as large, and the number of cells has been increased. Also the electrode vessel volume and the size of the electrodes must be increased accordingly. A special arrangement for sampling, making it possible to subdivide the contents of one compartment, has been introduced (Fig. 23). It consists of a pipette with a wide mouth, covered by a porous glass filter, which to a large extent eliminates convections when the liquid enters. The pipette is gradually lowered into one limb of the U-tube by the rack and pinion arrangement and its position with respect to the different boundaries is observed

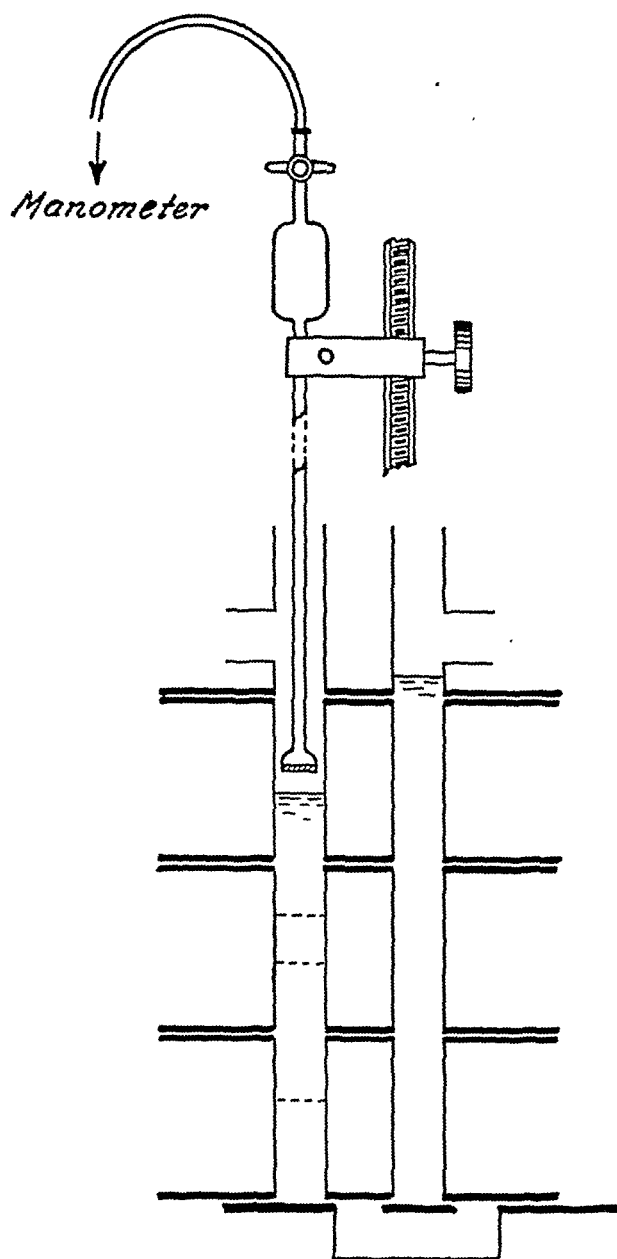


Fig. 23—Sampling device.

with the usual schlieren arrangement. Figure 22b shows the complete arrangement of the large apparatus. In preparative separation the so-called compensation arrangement has proved quite useful to increase the separation capacity of the electrophoresis tube (Fig. 24). In principle it depends upon the establishment of a slow and well-defined movement of the solution as a whole through the U-tube in a direction

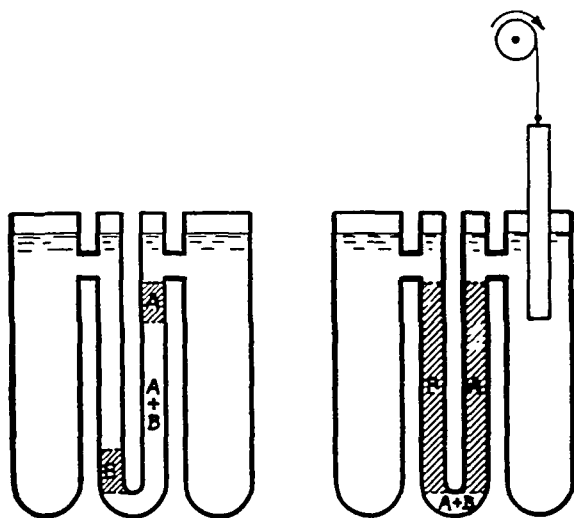


Fig. 24—Maximum separation obtainable without and with compensation.

opposite to that of the electrophoretic migration in order to keep the boundaries in the tube a sufficiently long time to attain as complete separation as possible.

The apparatus and procedure described have proved satisfactory for many separations, and have been used so far chiefly for serum fractionation. For many preparations where there are large differences in mobility and solutions of low conductivity can be used it seems probable that much simpler arrangements may work satisfactorily, especially if one is willing to sacrifice some of the convenience of this type of apparatus.

I may add that we also have a micro-cell (Fig. 25) with only a 2 cc. capacity, which has proved useful when only very small amounts of material are available.

In conclusion, I should like to say something about the limitations in the use of electrophoretic methods. It is well known that many large molecules, for example many polysaccharides, carry no charge and these, of course, fall entirely outside the scope of the method, except that their inability to move in an electric field at any pH is often quite useful to differentiate them as a group from other substances, as well as to separate them in quantity from other components in the mixture. To protein chemists it is a well-known fact that a very large number of albumins have isoelectric points in the neighborhood of pH 4.7. It has,

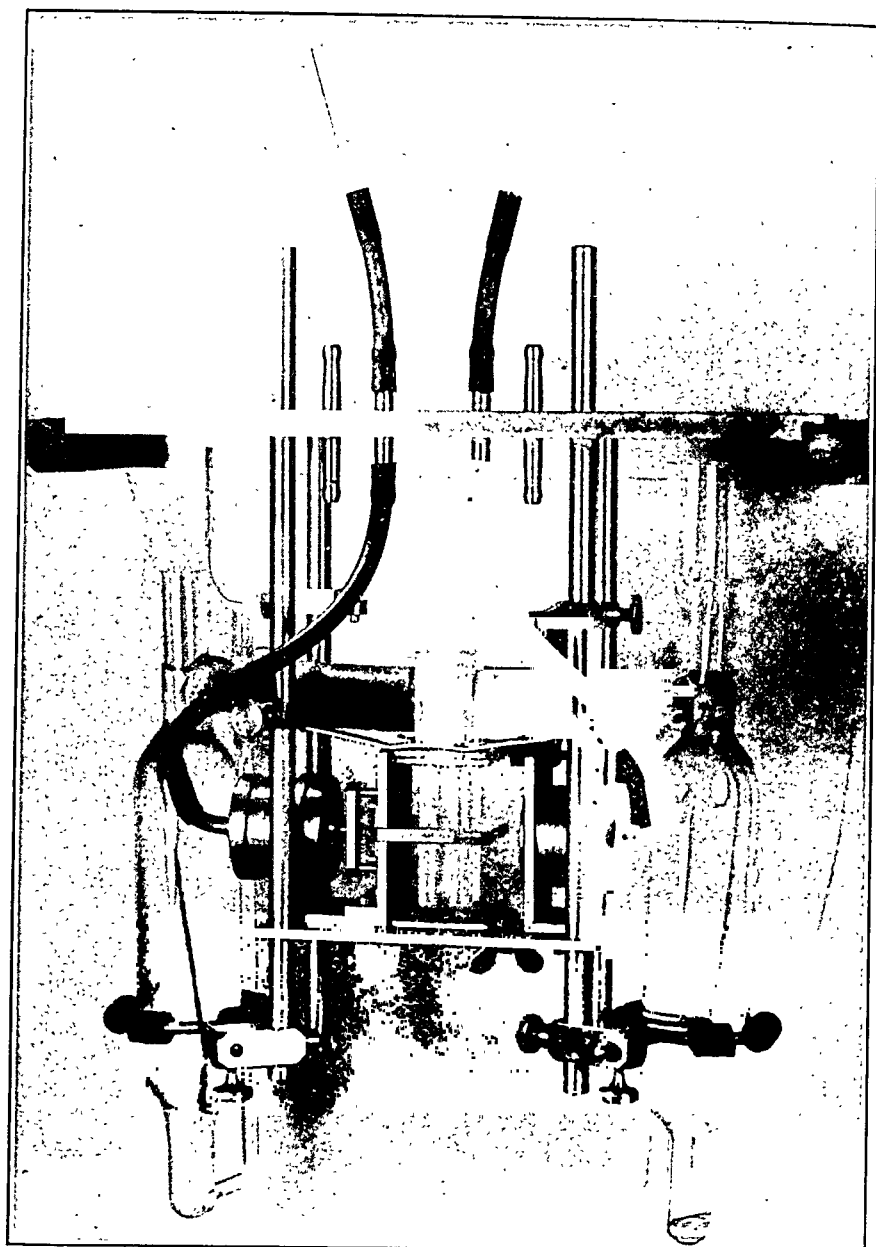


Fig. 25—Micro-electrophoresis apparatus (capacity 2 cc.).

however, been found that two proteins very seldom show the same mobility over the entire pH-stability range; usually the differences are most marked at an appreciable distance from the isoelectric point. Biologically related proteins are, of course, mostly quite similar, even if striking differences are encountered here too. The respiratory pigments

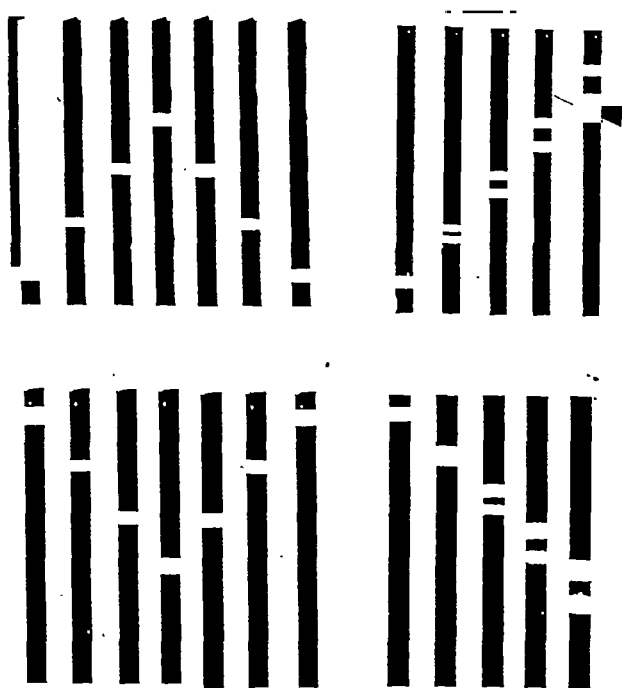


Fig. 26—Electrophoresis of guinea hen egg albumin (left) and a mixture of guinea hen and duck egg albumins (right). (From Landsteiner, Longworth and van der Scheer<sup>39</sup>).

of the two snails, *Helix pomatia* and *Helix nemoralis* (hemocyanins) at pH 6.8 in 0.1 phosphate buffer show mobilities of 3.08 and 5.27 respectively (Pedersen;<sup>38</sup> Tiselius and Horsfall<sup>23,24</sup>). Adair found that maternal and fetal hemoglobin from sheep could be distinguished easily (unpublished work). Landsteiner, Longworth and van der Scheer<sup>39</sup> could differentiate egg albumins from the two groups of birds Anseriformes and Galliformes (Fig. 26). Within each group the species differences were, however, insufficient to give a distinct separation even if in some cases a broadening of the schlieren bands could be seen. As these authors emphasize, the species differences may often be located in groups which are electrically inert. There is hardly any doubt that serological reactions and solubilities of crystalline material are more specific properties than the electrophoretic mobility, even if the separation by these methods may not always be as clear-cut as that obtained by electrophoresis.

The greatest difficulty in preparative electrophoretic separation seems to be the spreading of the boundaries when they migrate over large distances. This spreading is much larger than can be accounted for by *diffusion only*, and, according to recent investigations by Horsfall and myself,<sup>24</sup> seems to be largely reversible, indicating either that most of the proteins investigated are still not quite homogenous or that an unknown source of disturbance is present in most of our experiments. If it were not for this effect, the possibilities of electrophoretic separation would be much greater, at least if sufficiently long times can be used for the experiments. It should be remembered that the separation is proportional to the time, whereas the diffusion is proportional only to the square root of time.

Another difficulty, which is of very great importance in quantitative work when mobilities have to be calculated or the relative amounts of the components estimated, is caused by the interference of the migration of the ions of the medium and is particularly important in solutions of high protein and low salt concentration. The differences between descending and ascending diagrams and the non-moving boundaries are caused by these effects. Time does not allow me to enter upon a discussion of these phenomena here. It may be sufficient, however, to emphasize the importance of an accurate knowledge of these effects. An excellent treatment of the subject has been given in a paper by Henry and Brittain<sup>12</sup> published some years ago.

Effects of this kind are also responsible for the difficulties encountered when it is tried to extend the use of electrophoretic methods to substances of low molecular weight like amino acids and the smaller polypeptides.

From what I have said I hope I have been able to demonstrate to you that the application of electrophoresis methods opens up some new possibilities of studying the constitution of native fluids under conditions which are at least somewhat closer to those prevailing in the native state than if the common, more drastic methods are applied. I believe that progress in this field will depend to a large extent upon the development of the experimental technique and upon the proper understanding of the significance of the results and the limitations of the method. This field should prove particularly fruitful for the collaboration of research workers in physical chemistry, biology, and medicine in a manner which has proved so valuable for many other problems of modern science.

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# *Karo in Infant Diarrhea*

## **1. *Diminishing Diarrhea***

KARO prevents the flooding of the intestinal tract with excessive amounts of easily fermentable sugars because the dextrose and maltose components are quickly absorbed and the difficultly fermentable dextrin is gradually transformed into monosaccharides.

## **2. *Treating an Attack***

KARO may be added in suitable amounts to acidified, skimmed or evaporated milk without any tendency for fluid to be drawn into the intestines or be increased in the stools.

## **3. *Feeding in Convalescence***

KARO is gradually increased in the formula, according to individual indications, in order to provide the high energy requirement necessary to combat exhaustion. KARO is well tolerated, easily digested and non-irritating to the intestinal tract.



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